mp 103-106 °C; FDMS 610 (M^+); Anal. Calcd for $C_{38}H_{46}N_2O_3S \cdot 1.48H_2O$: C, 71.59; H, 7.74; N, 4.39. Found: C, 71.59; H, 7.44; N, 4.32.

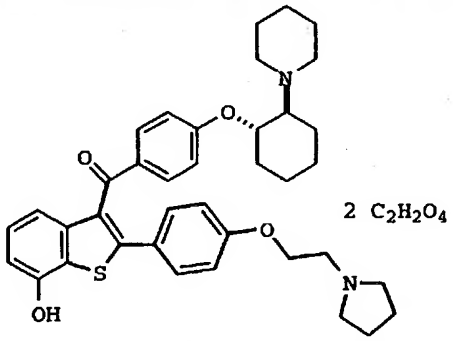
Part B. (±)-5-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared from the free base by essentially following the procedures detailed in Example 21, Part C.

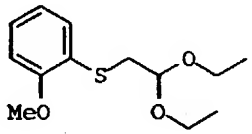
mp 172-176 °C (dec); FDMS 611 (M+); Anal. Calcd for $C_{38}H_{46}N_2O_3S \cdot 2C_2H_2O_4 \cdot 1.5H_2O$: C, 61.67; H, 6.53; N, 3.42. Found: C, 61.41; H, 6.21; N, 3.40.

Example 75

Preparation of (±)-7-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

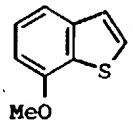


Part A. 2-Methoxybenzenethioacetaldehyde Diethyl Acetal.



The title compound was prepared in 90% crude yield from 2-methoxybenzenethiol by essentially following the procedures detailed in Graham, S.L., et. al. *J. Med. Chem.* **1989**, *32*, 2548-2554.

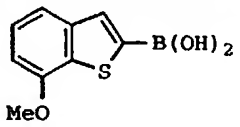
Part B. 7-Methoxybenzo[*b*]thiophene.



To a biphasic mixture of polyphosphoric acid (PPA; 64.1 g) and 600 mL of dry chlorobenzene heated to reflux at 140 °C was added dropwise 2-methoxybenzenethioacetaldehyde diethyl acetal (Part A) (30.0 g, 117 mmol) in 75 mL of chlorobenzene over a period of 1.5 h. The dark green biphasic mixture was stirred at reflux for an additional 1.5 h. The reaction mixture was cooled to room temperature and the organic layer was decanted off the PPA layer. The PPA layer was cooled to 0 °C and diluted with 500 mL of H_2O. This aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with 200 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified using a PrepLC with a gradient elution (0 to 7% Et_2O in hexanes) to afford 10.3 g (63.1 mmol, 54%) of a green oil.

FDMS 164 (M^+); Anal. Calcd for $C_9H_8OS \cdot 0.06CH_2Cl_2$: C, 64.27; H, 4.83. Found: C, 64.15; H, 4.81.

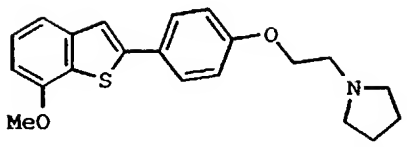
Part C. 7-Methoxybenzo[*b*]thiophene-2-boronic Acid.



The title compound was prepared in 44% yield (51% SM recovery) by essentially following the procedures in Example 1, Part A from 7-methoxy[*b*]benzothiophene (Part B).

mp 272-275 °C; FDMS 569; Anal. Calcd for $C_9H_9BO_3S$: C, 51.96; H, 4.36; N, 0.00. Found: C, 51.71; H, 4.15; N, 0.00.

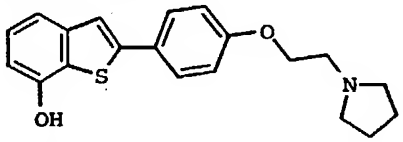
Part D. 7-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 31% yield by essentially following the procedures outlined in Example 1, Part B from 7-methoxybenzo[*b*]thiophene-2-boronic acid (Part C).

mp 88-90 °C; FDMS 353 (M^+); Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.17; H, 6.58; N, 3.83.

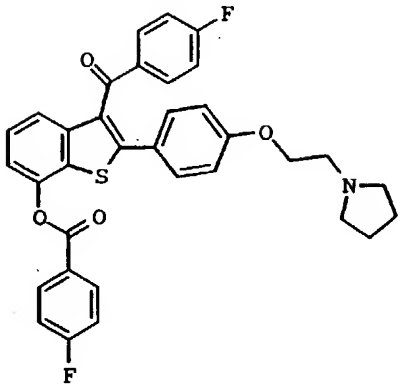
Part E. 7-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared by essentially following the procedures outlined in Example 21, Part B from 7-methoxy-benzo[*b*]thiophene (Part D) and recrystallized from EtOAc-hexanes to afford 944 mg (2.78 mmol, 56%) of light orange needle-like crystals.

mp 180-183 °C; FDMS 339 (M+); Anal. Calcd for $C_{20}H_{21}NO_2S \cdot 0.3H_2O$: C, 69.66; H, 6.31; N, 4.06. Found: C, 69.62; H, 6.21; N, 4.46.

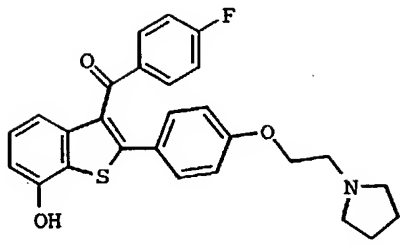
Part F. 3-(4-Fluorophenyl)carbonyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-7-yl 4-Fluorobenzoate.



To a slurry of 7-hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene (Part E) (244 mg, 0.808 mmol) in 5.0 mL of anhydrous dichloroethane was added 4-fluorobenzoyl chloride (105 µL, 0.888 mmol) at room temperature. The white slurry was stirred at room temperature for 3 h to form the intermediate ester. The reaction was then cooled to 0 °C and another 105 µL (0.888 mmol) of 4-fluorobenzoyl chloride was added, followed by addition of aluminum chloride (431 mg, 3.23 mmol) which turned the slurry into a dark red homogeneous solution. The reaction was slowly warmed to room temperature over 2 h and then stirred for 2.5 days. The reaction mixture was then poured into 20 mL of ice-cold 2.0 N NaOH solution. The mixture was then taken up in EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 4%(10% NH_4OH in MeOH)/CH_2Cl_2) to afford 408 mg (.700 mmol, 87%) of an off-white foam.

mp 64-68 °C; FDMS 583 (M+); Anal. Calcd for $C_{34}H_{27}F_2NO_4S \cdot 0.08CH_2Cl_2$: C, 69.33; H, 4.64; N, 2.37. Found: C, 69.36; H, 4.61; N, 2.01.

Part G. 4-Fluorophenyl 7-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



To a slurry of NaH (14.4 mg, 0.171 mmol, 60% dispersion in mineral oil) in 0.5 mL of anhydrous THF (or DMF) was added (±)-*trans*-2-(1-piperidyl)cyclohexanol in 0.5 mL of THF (or DMF) via a cannula. The reaction mixture was warmed with a heat gun to initialize the alkoxide formation and then stirred at room temperature for 2 h. The slurry was cooled to 0 °C and to this was added dropwise 4-fluorobenzoate (Part F) (100 mg, 0.171 mmol) in 0.5 mL of THF (or DMF). The reaction was stirred at 0 °C for 1 h and then allowed to warm to room temperature while stirring for 45 min. The reaction was quenched at 0 °C with 15 mL of H_2O. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 70:27:3 THF-hexanes-Et_3N) to afford 67.9 mg (.147 mmol, 86%) of a brown solid.

mp 138-142 °C, FDMS 462 (M+); Anal. Calcd for $C_{27}H_{24}FNO_3S \cdot 0.57H_2O$: C, 68.73; H, 5.37; N, 2.97. Found: C, 68.95; H, 5.66; N, 3.30.

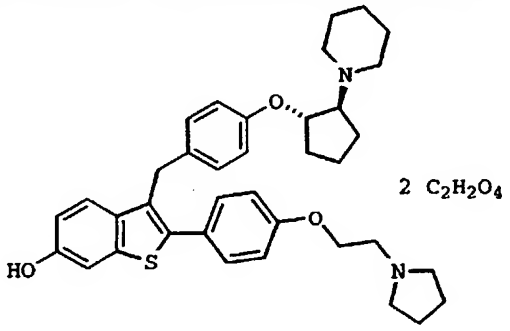
Part H. (±)-7-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

The free base of the title compound was prepared in 18% yield by essentially following the procedures in Example 72, Part E, from 4-fluorophenyl ketone (Part G) and (±)-*trans*-2-(1-piperidyl)cyclohexanol (Example 20 Part A). The dioxalate was then prepared by essentially following procedures in Example 21, Part C from the free base.

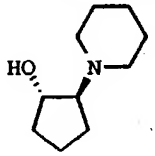
FDMS 625 (M+); Anal. Calcd for $C_{38}H_{44}N_2O_4S \cdot 2.5C_2H_2O_4 \cdot 3.2H_2O$: C, 56.91; H,6.15; N, 3.09. Found: C, 56.61; H, 5.80; N, 3.47.

Example 76

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclopentyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



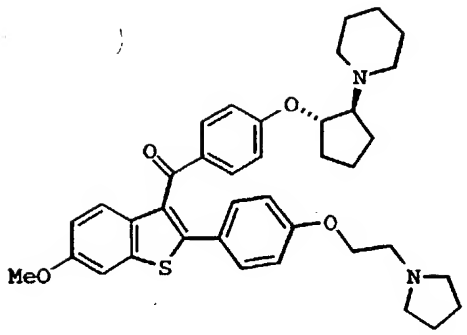
Part A. (±)-*trans*-2-(1-Piperidyl)cyclopentanol.



The title compound was prepared in 81% yield from cyclopentene oxide and piperidine by essentially following the procedures outlined in Example 20, Part A.

FDMS 169.1 (M^+); Anal. Calcd for $C_{10}H_{19}NO \cdot 0.24H_2O$: C, 69.19; H, 11.31; N, 8.07. Found: C, 69.19; H, 11.40; N, 8.21.

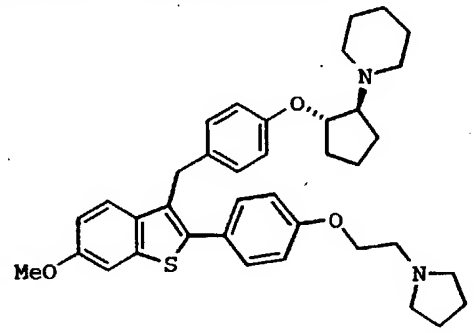
Part B. (±)-6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[(±)-*trans*-2-(1-Piperidyl)cyclopentyl]oxy]phenyl Ketone.



The title compound was prepared in 70% yield by essentially following the procedures outlined in Example 72, Part E, from 4-fluorophenyl 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (Example 59, Part A) and (±)-*trans*-2-(1-piperidyl)-cyclopentanol (Part A).

mp 68-72 °C; FDMS 625 (M^+); Anal. Calcd for $C_{38}H_{44}N_2O_4S$: C, 73.05; H, 7.10; N, 4.48. Found: C, 73.27; H, 6.96; N, 4.30.

Part C. (±)-6-Methoxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclopentyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene.



The title compound was prepared in 57% yield from the ketone (Part B) by essentially following the procedures detailed in Example 21, Part A.

mp 61-64 °C; FDMS 611 (M+); Anal Calcd for $C_{38}H_{46}N_2O_3S \cdot 0.39H_2O$: C, 73.87; H, 7.63; N, 4.53. Found: C, 73.85; H, 7.53; N, 4.83.

Part D. (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclopentyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

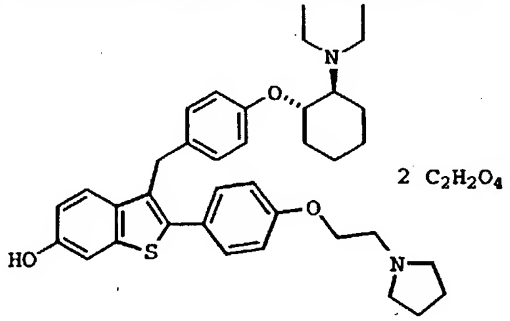
The free base of title compound was prepared in 79% yield from the methoxybenzo[*b*]thiophene (Part C) by essentially following the procedures detailed in Example 21, Part B.

The title compound was prepared by essentially following the procedures detailed in Example 21, Part C.

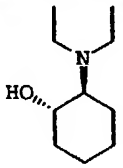
mp 145-150 °C; FDMS 597 (M^+); Anal. Calcd for $C_{37}H_{44}N_2O_3S \cdot 2.1C_2H_2O_4 \cdot 1.6H_2O$: C, 60.74; H, 6.36; N, 3.44. Found: C, 60.41; H, 6.46; N, 3.37.

Example 77

Preparation of (±)-3-[4-[[*trans*-2-(Diethylamino)-cyclohexyl]oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



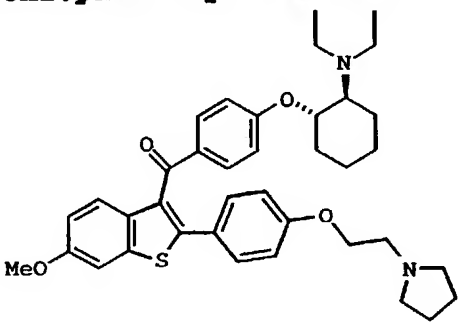
Part A. (±)-*trans*-2-(Diethylamino)cyclohexanol.



The title compound was prepared from N,N-diethylamine and cyclohexene oxide by essentially following the procedures outlined in Example 20, Part A.

FDMS 171 (M+, base); Anal. Calcd for $C_{10}H_{21}NO \cdot 0.26CH_2Cl_2$: C, 63.73; H, 11.22; N, 7.24. Found: C, 63.80; H, 11.35; N, 7.52.

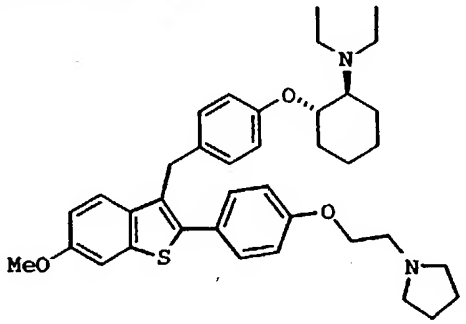
Part B. (±)-4-[[*trans*-2-(Diethylamino)cyclohexyl]-oxy]phenyl 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl Ketone.



The title compound was prepared in 67% yield by essentially following the procedures outlined in Example 72, Part E, from 4-fluorophenyl 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (Example 59, Part A) and (±)-*trans*-2-(diethylamino)-cyclohexanol (Part A).

FDMS 627 (M^+); Anal. Calcd for $C_{38}H_{46}N_2O_4S$: C, 72.81; H, 7.40; N, 4.47. Found: C, 73.06; H, 7.44; N, 4.65.

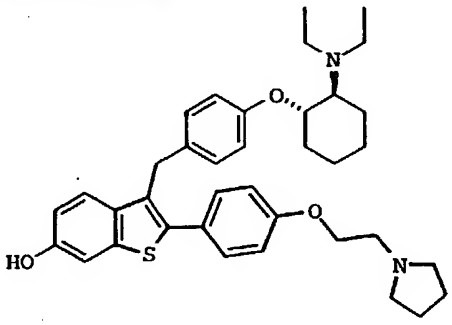
Part C. (±)-3-[4-[[*trans*-2-(Diethylamino)cyclohexyl]-oxy]benzyl]-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 79% yield from the ketone (Part B) by essentially following the procedures detailed in Example 21, Part A.

FDMS 613 (M^+); Anal. Calcd for $C_{38}H_{48}N_2O_3S$: C, 74.47; H, 7.89; N, 4.57. Found: C, 74.49; H, 8.18; N, 4.66.

Part D. (±)-3-[4-[[*trans*-2-(Diethylamino)cyclohexyl]-oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 73% yield from the methoxybenzo[*b*]thiophene (Part C) by essentially following the procedures detailed in Example 21, Part B.

mp 95-100 °C; FDMS 599 (M+); Anal. Calcd for $C_{37}H_{46}N_2O_3S \cdot 0.2CH_2Cl_2$: C, 72.55; H, 7.59; N, 4.55. Found C, 72.21; H, 7.59; N, 4.87.

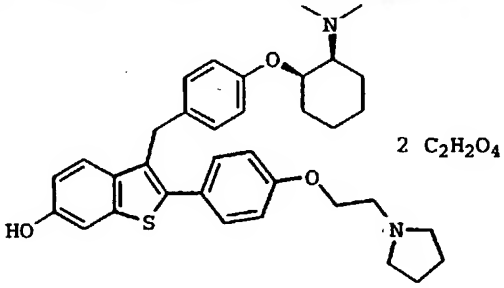
Part E. (±)-3-[4-[[*trans*-2-(Diethylamino)cyclohexyl]-oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared from the free base (Part D) by essentially following the procedures detailed in Example 21, Part C.

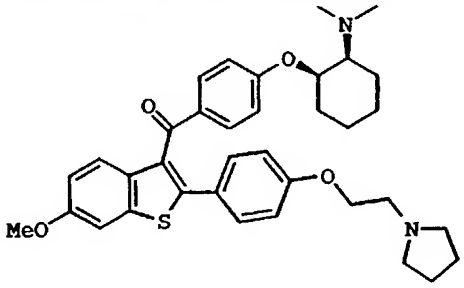
mp 143-146 °C; FDMS 599 (M^+); Anal. Calcd for $C_{37}H_{46}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 1.8H_2O$: C, 60.64; H, 6.66; N, 3.45. Found: C, 60.63; H, 6.31; N, 3.26.

Example 78

Preparation of (±)-3-[4-[[*cis*-2-(Dimethylamino)-cyclohexyl]oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



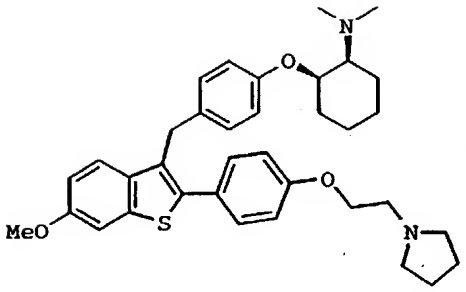
Part A. (±)-4-[*cis*-2-(Dimethylamino)cyclohexyloxy]-phenyl 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl Ketone.



The title compound was prepared in 71% yield by essentially following the procedures outlined in Example 72, Part E, from 4-fluorophenyl 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (Example 59, Part A) and (±)-*cis*-2-(dimethylamino)-cyclohexanol.

mp 61-64 °C; FDMS 599 (M+); Anal. Calcd for $C_{36}H_{42}N_2O_4S$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.15; H, 7.30; N, 4.64.

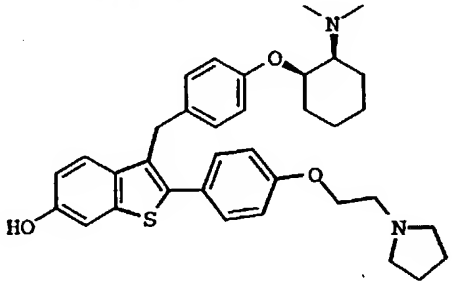
Part B. (±)-3-[4-[[*cis*-2-(Dimethylamino)cyclohexyl]-oxy]benzyl]-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 57% yield from the ketone (Part A) by essentially following the procedures detailed in Example 21, Part A.

FDMS 585 (M^+); Anal. Calcd for $C_{36}H_{44}N_2O_3S \cdot 0.27CH_4O$: C, 73.41; H, 7.66; N, 4.72. Found: C, 73.62; H, 7.74; N, 4.32.

Part C. (±)-3-[4-[[*cis*-2-(Dimethylamino)cyclohexyl]-oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 75% yield from the methoxybenzo[*b*]thiophene (Part B) by essentially following the procedures detailed in Example 21, Part B.

mp 95-98 °C; FDMS 571 (M^+); Anal. Calcd for $C_{35}H_{42}N_2O_3S$: C, 73.65; H, 7.42; N, 4.91. Found C, 73.39; H, 7.63; N, 4.78.

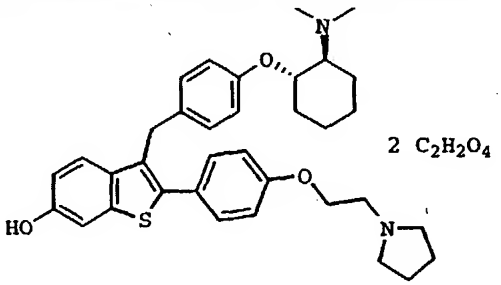
Part D. (±)-3-[4-[[*cis*-2-(Dimethylamino)cyclohexyl]-oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared from the free base (Part C) by essentially following the procedures detailed in Example 21, Part C.

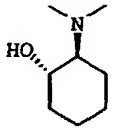
mp 103-106 °C (dec.); FDMS 571 (M^+); Anal. Calcd for $C_{35}H_{42}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 1.7H_2O$: C, 59.94; H, 6.37; N, 3.58. Found: C, 59.81; H, 6.09; N, 3.44.

Example 79

Preparation of (±)-3-[4-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

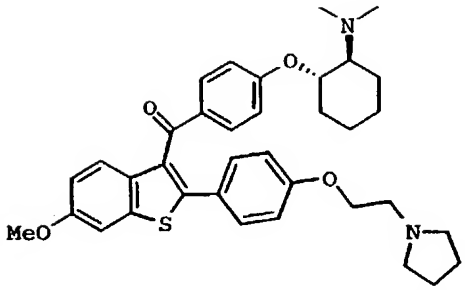


Part A. (±)-*trans*-2-(Dimethylamino)cyclohexanol.



To a solution of cyclohexene oxide (3.64 mL, 36.0 mmol) in 30 mL of dry methanol was added dropwise 2.0 M dimethylamine in THF (15.0 mL, 30.0 mmol). The reaction mixture was stirred at 0 °C for 4 h. The solution was then warmed to room temperature and stirred for 18 h. The reaction mixture was then concentrated under reduced pressure to afford 1.11 g (26% crude yield) of the crude product which was used in the following reaction without purification.

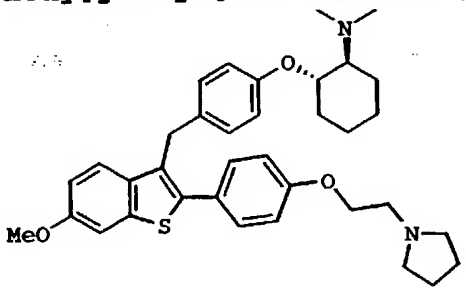
Part B. (±)-4-[[*trans*-2-(Dimethylamino)cyclohexyl]-oxy]phenyl 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl Ketone.



The title compound was prepared in 77% yield by essentially following the procedures outlined in Example 72, Part E, from 4-fluorophenyl 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (Example 59, Part A) and (±)-*trans*-2-(dimethylamino)cyclohexanol (Part A).

mp 65-70 °C; FDMS 599 (M^+); Anal. Calcd for $C_{36}H_{42}N_2O_4S$: C, 72.21; H, 7.07; N, 4.68. Found: C, 71.98; H, 6.96; N, 4.44.

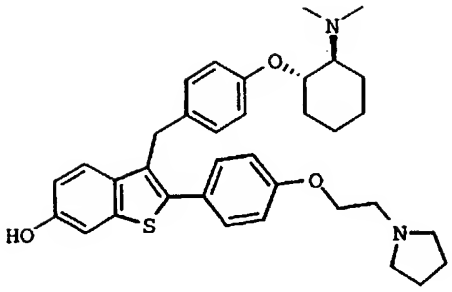
Part C. (±)-3-[4-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]benzyl]-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene.



The title compound was prepared in 66% yield from the ketone (Part B) by essentially following the procedures detailed in Example 21, Part A.

mp 58-61 °C, FDMS 585 (M^+); Anal. Calcd for $C_{36}H_{44}N_2O_3S$: C, 73.94; H, 7.58; N, 4.79. Found: C, 74.19; H, 7.55; N, 5.07.

Part D. (±)-3-[4-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene.



The title compound was prepared in 77% yield from the methoxybenzo[*b*]thiophene (Part C) by essentially following the procedures detailed in Example 21, Part B.

mp 97-102 °C; FDMS 571 (M^+); Anal. Calcd for $C_{35}H_{42}N_2O_3S \cdot 0.19CH_2Cl_2$: C, 72.01; H, 7.28; N, 4.77. Found C, 72.04; H, 7.32; N, 4.43.

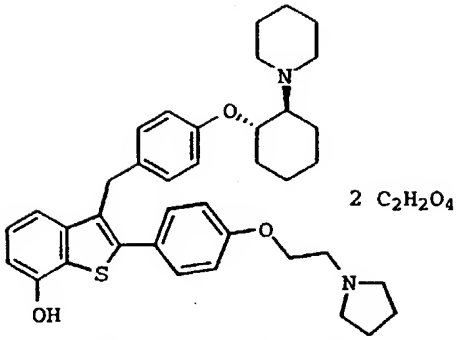
Part E. (±)-3-[4-[[*trans*-2-(Dimethylamino)cyclohexyl]oxy]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared from the free base (Part D) by essentially following the procedures detailed in Example 21, Part C.

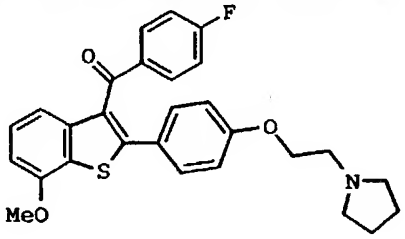
mp 104-106 °C (dec.); FDMS 571 (M^+); Anal. Calcd for $C_{35}H_{42}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 1.2H_2O$: C, 60.44; H, 6.41; N, 3.51. Found: C, 60.07; H, 6.26; N, 3.21.

Example 80

Preparation of (±)-7-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



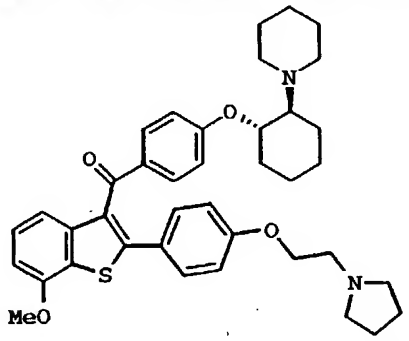
Part A. 4-Fluorophenyl 7-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



To a suspension of powdered KOH (177 mg, 3.15 mmol) in 1.6 mL of dry DMSO was added 4-fluorophenyl 7-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (350370) (Example 75, Part G) (364 mg, .788 mmol) at room temperature. The reaction mixture turned orange in color. To the alkoxide was added slowly methyl iodide (49 µL, .79 mmol) over a period of 15 min. The reaction mixture was then stirred for 1.5 h. Another portion of MeI (20 µL, .32 mmol) was added, stirred for 1.5 h., followed by another addition of 20 µL (0.32 mmol) of MeI and stirring for an additional 30 min at room temperature. The rection mixture was then poured into 20 mL of H_2O. This mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O (5 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was then purified by flash chromatography (silica gel, 4%[10% NH_4OH in MeOH]/CH_2Cl_2) to afford 108 mg (.226 mmol, 29%) of a white foam.

FDMS 475 (M^+); Anal. Calcd for $C_{28}H_{26}FNO_3S$: C, 70.71; H, 5.51; N, 2.94. Found: C, 70.48; H, 5.77; N, 2.72.

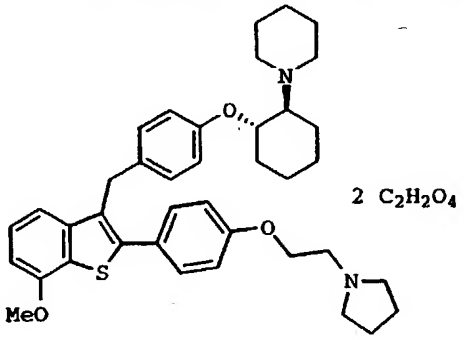
Part B. (±)-7-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 74% yield by essentially following the procedures outlined in Example 72, Part E, from the 4-fluorophenyl ketone (BZ4-GCY-222) (Part A) and (±)-*trans*-2-(1-piperidyl)cyclohexanol (Example 20, Part A).

mp 66-69 °C; FDMS 639 (M+); Anal. Calcd for $C_{36}H_{46}N_2O_4S$: C, 73.32; H, 7.26; N, 4.38. Found: C, 73.60; H, 7.53; N, 4.65.

Part C. (±)-7-Methoxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



The free base of the title compound was prepared in 63% yield from the ketone (Part B) by essentially following the procedures detailed in Example 21, Part A. The title compound was prepared by essentially following the procedures outlined in Example 21, Part C from the free base obtained.

FDMS 625 (M+), Anal. Calcd for $C_{39}H_{48}N_2O_3S \cdot 2.1C_2H_2O_4 \cdot 1.4H_2O$: C, 61.83; H, 6.61; N, 3.34. Found: C, 61.49; H, 6.58; N, 3.44.

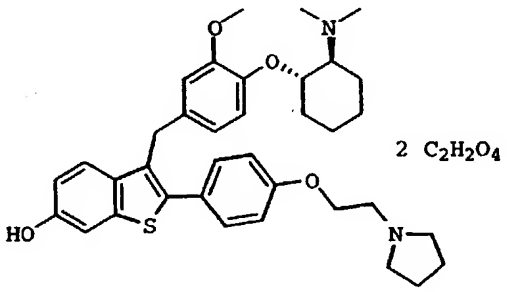
Part D. (±)-7-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The free base of the title compound was prepared in 76% yield from the methoxybenzothiophene (free base of Part C) by essentially following the procedures detailed in Example 21, Part B. The title compound was prepared by essentially following the procedures outlined in Example 21, Part C from the free base obtained.

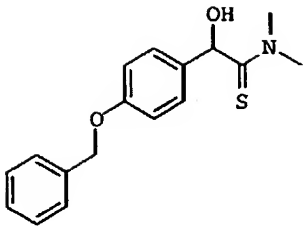
FDMS 611 (M^+); Anal. Calcd for $C_{38}H_{46}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 3.3H_2O$: C, 59.35; H, 6.71; N, 3.30. Found: C, 59.33; H, 6.66; N, 3.45.

Example 81

Preparation of (±)-3-[4-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]-3-methoxybenzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



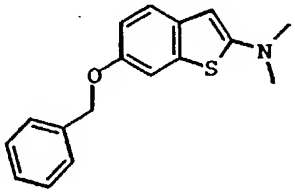
Part A. 4-Benzyloxy-α-hydroxy-N,N-(dimethyl)phenyl-thioacetamide.



To a solution of distilled diisopropylamine (22.9 mL, 175 mmol) in 400 mL of anhydrous THF at -78 °C was added 1.6 M *n*-butyllithium in hexanes (100 mL, 160 mmol) over a period of 45 min. The mixture was stirred at -78 °C for 1.5 h. To the solution was cannulated over a period of 1 h a solution of 4-benzyloxybenzaldehyde (30.9 g, 146 mmol) and N,N-dimethylthioformamide (13.7 mL, 160 mmol) in 100 mL of distilled THF. The reaction mixture was stirred at -78 °C for 16 h. The reaction was then quenched with 500 mL of saturated NH_4Cl solution. The mixture was extracted with EtOAc (3 x 1 L), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then recrystallyzed from EtOAc/hexanes to afford 20.0 g (66.5 mmol, 46%) of an off-white solid.

mp 104-107 °C; FDMS 301 (M+); Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.75; H, 6.35; N, 4.65. Found: C, 67.61; H, 6.37; N, 4.57.

Part B. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]-thiophene.

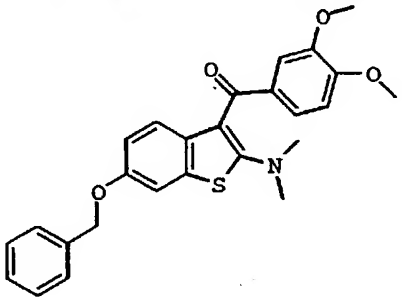


To a solution of thioacetamide (Part A) (500 mg, 1.66 mmol) in 65 mL of dry dichloroethane at room temperature was added dropwise methanesulfonic acid (0.54 ml, 8.3 mmol). The red reaction mixture was stirred for 1.5 h and then poured into 10 mL of saturated aqueous $NaHCO_3$ solution, followed by addition of 3 mL of H_2O, and stirred vigorously. The layers

were separated and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by flash chromatography (silica gel, 10% Et_2O/hexanes) to afford 327 mg (1.15 mmol, 70%) of a white solid.

mp 78-81 °C; FDMS 283 (M+); Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.22; H, 6.15; N, 4.89.

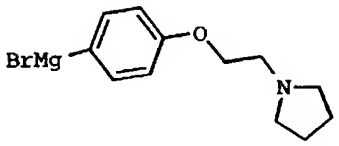
Part C. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3,4-Dimethoxyphenyl Ketone.



To a solution of 3,4-dimethoxybenzoyl chloride (1.250 g, 6.231 mmol) in 18 mL of chlorobenzene was added 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophene (Part B) (1.059 g, 3.738 mmol). The dark blue reaction mixture was then heated to 110 °C and stirred for 17 h by which time the solution turned to brown. The brown solution was then quenched at 0 °C with 30 mL of saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with 200 mL with brine, dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 50:50 EtOAc-hexanes) to afford 1.265 g (2.826 mmol, 76%) of a yellow foam.

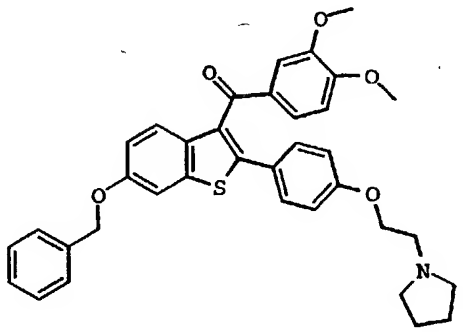
mp 69-72 °C; FDMS 447 (M+); Anal. Calcd for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13. Found: C, 69.93; H, 5.77; N, 3.25.

Part D. 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Magnesium Bromide.



To a solution of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine in 24.1 mL of freshly distilled THF was added 293 mg of magnesium turnings. The mixture was heated at reflux for 3 h or until all the magnesium was consumed to afford ~24.1 mL of 0.48 M Grignard reagent solution.

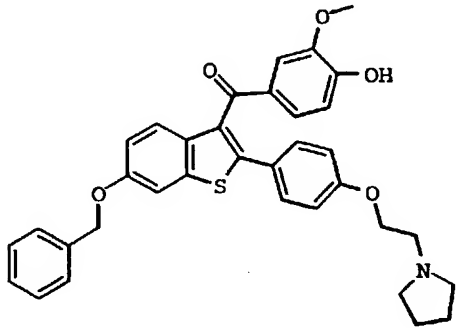
Part E. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3,4-Dimethoxyphenyl Ketone.



To the dimethylaminobenzo[*b*]thiophenyl ketone (Part C) (1.237 g, 2.763 mmol) in 30 ml of freshly distilled THF was added dropwise 0.48 M 4-[2-(1-pyrrolidinyl)ethoxy]phenyl magnesium bromide in THF (Part D) (8.63 mL, 4.14 mmol) at 0 °C. The resultant bright red solution was stirred at 0 °C for 2 h 15 min. The reaction was quenched at 0 °C with 30 mL of saturated aqueous NH_4Cl solution. The mixture was diluted with 15 mL of H_2O and extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and then purified by flash chromatography (silica gel, 60:37:3 THF-hexanes-Et_3N) to afford 1.507 g (2.538 mmol, 92%) of a yellow foam.

mp 74-77 °C; FDMS 593 (M+); Anal. Calcd for $C_{36}H_{35}NO_5S$: C, 72.83; H, 5.94; N, 2.36. Found: C, 72.91; H, 5.94; N, 2.62.

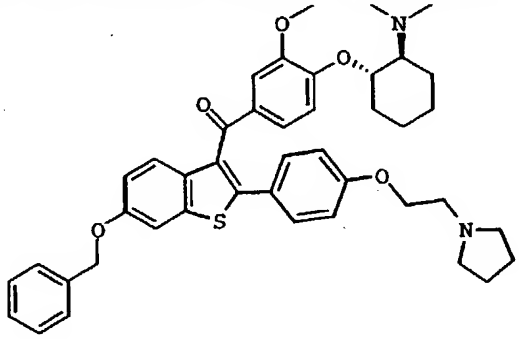
Part F. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-Hydroxy-3-methoxyphenyl Ketone.



To the 3,4-dimethoxyphenyl ketone (Part E) (1.496 g, 2.519 mmol) in 15 mL of dry DMF was added sodium thioethoxide (848 mg, 10.1 mmol), and the reaction mixture was stirred at 80 °C for 3h. The mixture was then cooled to 0 °C and quenched with 15 mL of saturated aqueous NH_4Cl solution. This mixture was extracted with $CHCl_3$ (3 x 150 mL). The combined organic layers were washed with 450 mL of H_2O and 150 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 6%[10% NH_4OH in MeOH]/CH_2Cl_2) to afford 1.251 g (2.159 mmol, 86%) of a yellow foam.

FDMS 579 (M+); Anal. Calcd for $C_{35}H_{33}NO_5S$: C, 72.52; H, 5.74; N, 2.42. Found: C, 72.63; H, 5.73; N, 2.64.

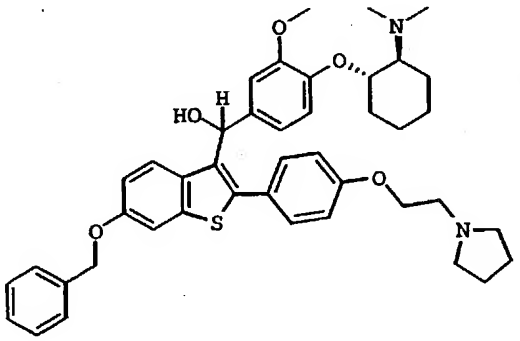
Part G. (±)-6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[*trans*-2-(Dimethylamino)cyclohexyl]oxy-3-methoxyphenyl Ketone.



The title compound was prepared in 93% yield by essentially following the procedures outlined in Example 20, Part B from the phenol (Part F) and (±)-*trans*-2-(dimethylamino)cyclohexanol (Example 79, Part A).

mp 66-69 °C; FDMS 705 (M+); Anal. Calcd for $C_{43}H_{48}N_2O_5S \cdot 0.62NH_5O$: C, 71.08; H, 7.09; N, 5.05. Found: C 70.88; H, 6.76; N, 4.65.

Part H. (±)-6-Benzyloxy-α-[4-[[*trans*-2-(dimethylamino)cyclohexyl]oxy]-3-methoxyphenyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-3-methanol.



The title compound was prepared in by essentially following the procedures outlined in Example 31, Part B from the ketone (Part G). The crude product was purified by flash chromatography (silica gel, 10%[10% NH_4OH in MeOH]/ CH_2Cl_2) to afford 418 mg (.591 mmol, 69%) of a white foam.

FDMS 708 (M+1); Anal. Calcd for $C_{43}H_{50}N_2O_5S \cdot 0.22CH_2Cl_2$: C, 71.54; H, 7.12; N, 3.86. Found: C, 71.52; H, 7.31; N, 4.06.

Part I. (±)-3-[4-[[*trans*-2-(Dimethylamino)cyclohexyl]-oxy]-3-methoxybenzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

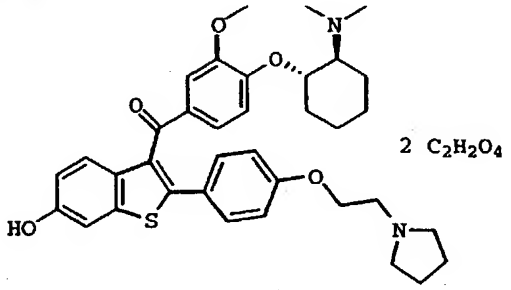
The 6-benzyloxy protected title compound was prepared from the disubstituted methanol (Part H) by essentially following procedures outlined in Example 31, Part C. A slurry of the crude (±)-6-benzyloxy-3-[4-[[*trans*-2-

(dimethylamino)cyclohexyl]oxy]-3-methoxybenzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (374 mg, .542 mmol) and Pd/C (10%, 375 mg) in 5.4 mL of a 1:1 mixture of THF-EtOH was stirred under positive hydrogen pressure (from balloon) for 19 h. The reaction mixture was filtered through a pad of diatomaceous earth and washed with THF. The filtrate was then concentrated under reduced pressure and the residue was flash chromatographed (silica gel, 10%[10% NH_4OH in MeOH]/CH_2Cl_2) to afford 200 mg (.333 mmol, 61% from alcohol) of an off-white foam. The title compound was then prepared by essentially following the procedures outlined in Example 21, Part C from the free base.

mp 167 °C (dec.); FDMS 601 (M+); Anal. Calcd for $C_{36}H_{44}N_2O_4S \cdot 1.83C_2H_2O_4$: C, 62.22; H, 6.27; N, 3.66. Found: C, 62.26; H, 6.40; N, 3.28.

Example 82

Preparation of (±)-4-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]-3-methoxyphenyl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

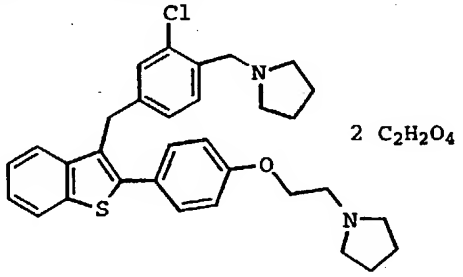


The title compound was prepared from the free base (Example 81, Part G) by essentially following the procedures outlined in Example 81, Part I and Example 21, Part C.

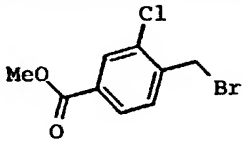
mp 170 °C (dec.); FDMS 615 (M+); Anal. Calcd for $C_{36}H_{42}N_2O_5S \cdot 1.82C_2H_2O_4$: C, 61.15; H, 5.91; N, 3.60. Found: C, 61.12; H, 6.05; N, 3.66.

Example 83

Preparation of 3-[3-Chloro-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.



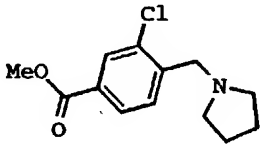
Part A. Methyl 4-Bromomethyl-3-chlorobenzoate.



The title compound was prepared in 56% yield by essentially following the procedure outlined in the first part of Example 37, Part A, from methyl 3-chloro-4-methylbenzoate.

FDMS 264 (M+); Anal. Calcd for $C_9H_8BrClO_2$: C, 41.02; H, 3.06. Found: C, 41.10; H, 3.10.

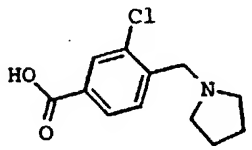
Part B. Methyl 3-Chloro-4-[(1-pyrrolidinyl)methyl]-benzoate.



The title compound was prepared in 44% yield by essentially following the procedures outlined in the second part of Example 37, Part A, from methyl 4-bromomethyl-3-chlorobenzoate (Part A).

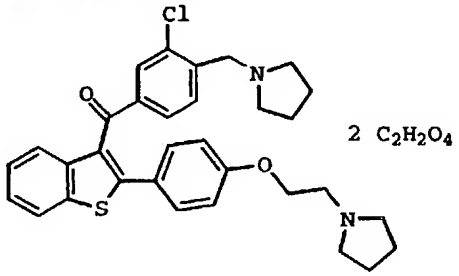
FDMS 253 (M+); Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.24; H, 6.11; N, 5.53.

Part C. 3-Chloro-4-[(1-pyrrolidinyl)methyl]benzoic Acid.



The title compound was prepared in 72% crude yield by essentially following the procedures outlined in Example 20, Part C, from methyl 3-chloro-4-[(1-pyrrolidinyl)methyl]-benzoate (Part B). This compound was used without purification.

Part D. 3-Chloro-4-[(1-pyrrolidinyl)methyl]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



The free base of the title compound was prepared in 55% yield by essentially following the procedures outlined in Example 1, Part C from 2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene (Example 4, Part A) and 3-chloro-4-[(1-pyrrolidiny)lmethyl]benzoic acid (Part C). The title compound was then prepared by essentially following the procedures outlined in Example 21, Part, C from the free base.

mp 97-102 °C; FDMS 544 (M-1); Anal. Calcd for $C_{32}H_{33}ClN_2O_2S \cdot 2.0C_2H_2O_4$: C, 59.62; H, 5.14; N, 3.86. Found: C, 59.41; H, 5.28; N, 3.90.

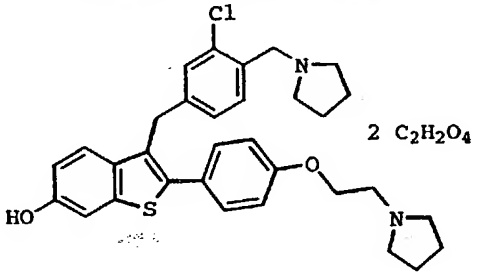
Part E. 3-[3-Chloro-4-[(1-pyrrolidinyl)methyl]-benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

The free base of the title compound was prepared in 57% yield by essentially following the procedures in Example 21, Part A from the ketone (free base of Part D). The title compound was prepared by essentially following the procedures outlined in Example 21, Part C from 3-[3-chloro-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.

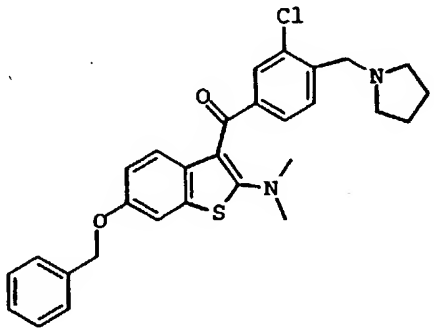
mp 126-130 °C dec.; FDMS 531 (M+); Anal. Calcd for $C_{32}H_{35}ClN_2OS \cdot 2.0C_2H_2O_4$: C, 60.80; H, 5.53; N, 3.94. Found: C, 60.63; H, 5.81; N, 3.87.

Example 84

Preparation of 3-[3-Chloro-4-[(1-pyrrolidinyl)methyl]-benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.



Part A. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-Chloro-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.

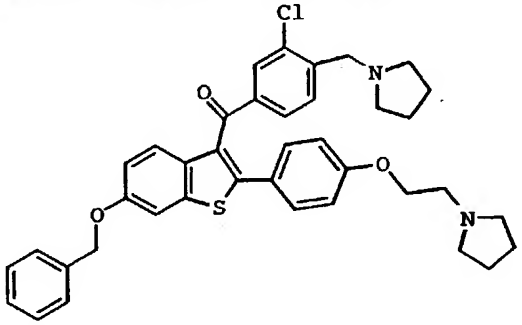


The title compound was prepared in 93% yield by essentially following the procedures outlined in Example 41, Part C (but using thionyl chloride to form the acid chloride)

from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophene (Example 81, Part B) and 3-chloro-4-[(1-pyrrolidinyl)methyl]benzoic acid (Example 83, Part C).

FDMS 504 (M-1); Anal Calcd. for $C_{29}H_{29}ClN_2O_2S$: C, 68.96; H, 5.79; N, 5.55. Found: C, 69.00; H, 5.62; N, 5.55.

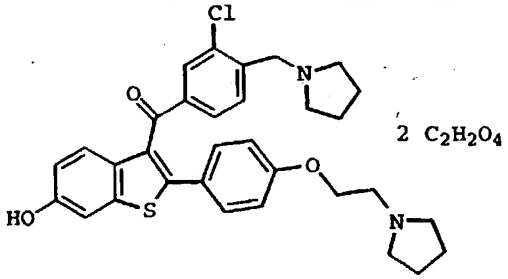
Part B. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Chloro-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



The title compound was prepared in 94% yield by essentially following the procedures in Example 81, Part E, from 4-[2-(1-pyrrolidinyl)ethoxy]phenyl magnesium bromide (Example 81, Part D) and 6-benzyloxy-2-(dimethylamino)-benzo[*b*]thiophen-3-yl 3-chloro-4-[(1-pyrrolidinyl)methyl]-phenyl ketone (Part A).

FDMS 651 (M+).

Part C. 3-Chloro-4-[(1-pyrrolidinyl)methyl]phenyl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl Ketone Dioxalate.



The free base of the title compound was prepared in 71% yield by essentially following the procedures outlined in Example 81, Part I from the ketone. The title compound was prepared by essentially following the procedure outlined in Example 21, Part C.

mp 174-178 °C; FDMS 561 (M^+); Anal. Calcd for $C_{32}H_{33}ClN_2O_3S \cdot 1.75C_2H_2O_4$: C, 59.33; H, 5.12; N, 3.78. Found: 59.33; H, 5.27; N, 3.90.

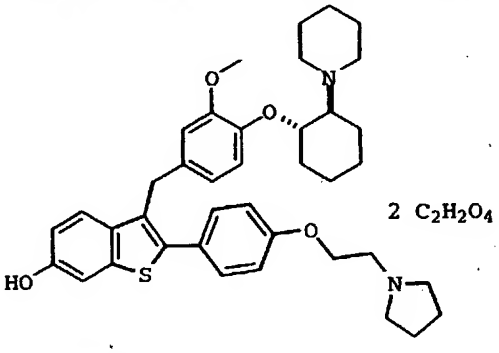
Part D. 3-[3-Chloro-4-[(1-pyrrolidinyl)methyl]-benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.

The free base of the title compound was prepared in 38% yield by essentially following the procedures outlined in Example 21, Part A, from the above ketone (Part C). The title compound was then prepared by essentially following the procedures outlined in Example 21, Part C.

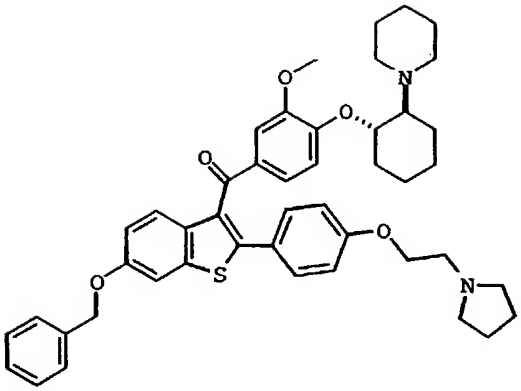
FDMS 547 (M^+); Anal. Calcd for $C_{32}H_{35}ClN_2O_2S \cdot 1.66C_2H_2O_4$: C, 60.90; H, 5.54; N, 4.02. Found: C, 60.90; H; 5.72; N 3.99.

Example 85

Preparation of (±)-6-Hydroxy-3-[3-methoxy-4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. (±)-6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 72% yield by essentially following the procedures outlined in Example 20, Part B, from 6-benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-hydroxy-3-methoxyphenyl ketone (Example 81, Part F) and (±)-*trans*-2-(1-piperidyl)-cyclohexanol (Example 20, Part A).

FDMS 746 (M^+); Anal. Calcd for $C_{46}H_{52}N_2O_5S \cdot 0.19CH_2Cl_2$: C, 72.89; H, 6.94; N, 3.68. Found: C, 72.84; H, 6.98; N, 4.03.

Part B. (±)-6-Hydroxy-3-[3-methoxy-4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

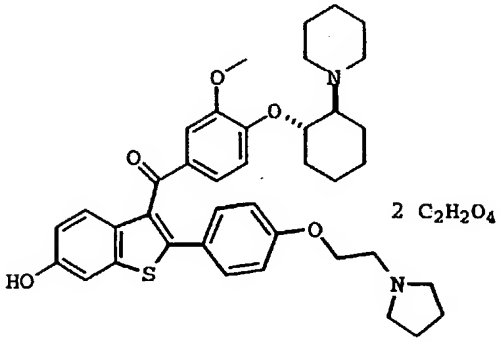
The free base of the title compound was prepared in 46% yield by essentially following the procedures outlined in Example 21, Part A and Example 81, Part I from the ketone (Part A). The title compound was then prepared by essentially following the procedure outlined in Example 21, Part C.

mp 167-171 °C (dec.); FDMS 641 (M^+); Anal. Calcd for $C_{39}H_{48}N_2O_4S \cdot 1.88C_2H_2O_4$: C, 63.39; H, 6.44; N, 3.46. Found: C, 63.39; H, 6.61; N, 3.27.

Example 86

Preparation of (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-

[[*trans*-2-(1-piperidyl)cyclohexy]loxy]phenyl Ketone Dioxalate.

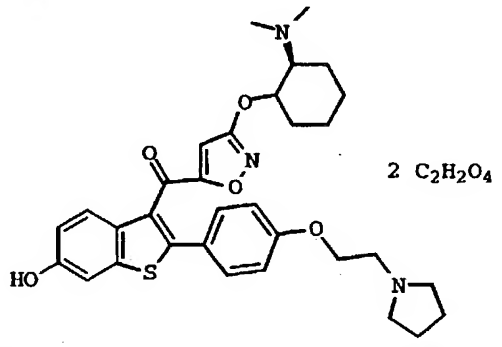


The free base of the title compound was prepared in 41% yield by essentially following the debenzylation procedure in Example 81, Part I, from the ketone (Example 85, Part A). The title compound was then prepared by essentially following the procedures in Example 21, Part C.

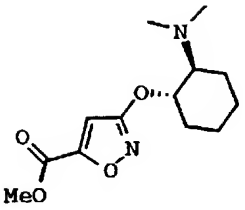
mp 151-155 °C; FDMS 655 (M^+); Anal. Calcd for $C_{39}H_{46}N_2O_5S \cdot 1.76C_2H_2O_4$: C, 62.79; H, 6.14; N, 3.44. Found: C, 62.56; H, 6.54; N, 3.31.

Example 87

Preparation of (±)-3-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]isoxazol-5-yl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



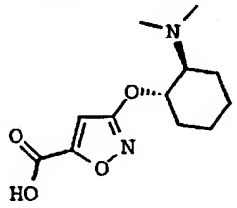
Part A. (±)-Methyl 3-[[*trans*-2-(Dimethylamino)-cyclohexyl]oxy]isoxazole-5-carboxylate.



The title compound was prepared in 73% yield by essentially following the procedures outlined in Example 20, Part B from methyl 3-hydroxyisoxazole-5-carboxylate and (±)-trans-2-(dimethylamino)cyclohexanol (Example 79, Part A).

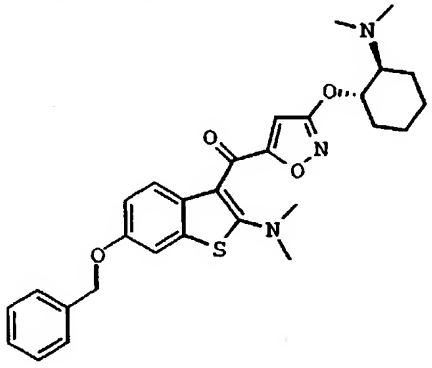
FDMS 268 (M+); Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.31; H, 7.51; N, 10.54.

Part B. (±)-3-[[*trans*-2-(Dimethylamino)cyclohexyl]-oxy]isoxazole-5-carboxylic Acid.



The title compound was prepared by essentially following the procedures outlined in Example 20, Part C, from the ester (Part A).

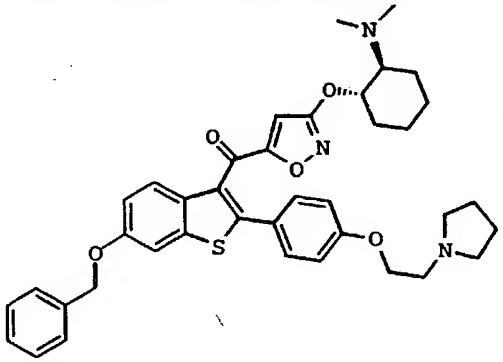
Part C. (±)-6-Benzyloxy-2-(dimethylamino)benzo[*b*]-thiophen-3-yl 3-[[*trans*-2-(Dimethylamino)cyclohexyl]-oxy]isoxazol-5-yl Ketone.



The title compound was prepared in 92% yield by essentially following the procedures outlined in Example 84, Part A from the isoxazole-5-carboxylic acid (Part B) and 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophene (Example 81, Part B).

FDMS 519 (M+); Anal. Calcd for $C_{29}H_{33}N_3O_4S \cdot 0.52H_2O$: C, 65.84; H, 6.49; N, 7.94. Found: C, 65.87; H, 6.12; N, 7.56.

Part D. (±)-6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-[[*trans*-2-(Dimethylamino)cyclohexyl]oxy]isoxazol-5-yl Ketone.



The title compound was prepared in 77% yield by essentially following the procedures outlined in Example 81, Part E from the ketone (Part C) and 4-[2-(1-pyrrolidinyl)-ethoxy]phenyl magnesium bromide (Example 81, Part D).

FDMS 666 (M+).

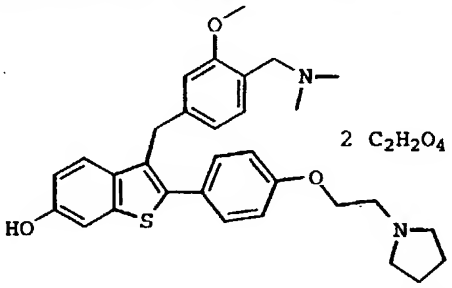
Part E. (±)-3-[[*trans*-2-(Dimethylamino)cyclohexyl]-oxy]isoxazol-5-yl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

The free base of the title compound was prepared in 51% yield by essentially following the debenzylation procedure outlined in Example 81, Part I from the ketone (Part D). The title compound was prepared by essentially following the procedures in Example 21, Part C.

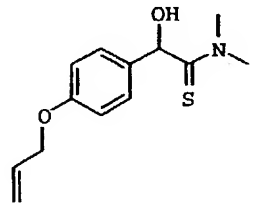
FDMS 576 (M+).

Example 88

Preparation of 3-[4-[(Dimethylamino)methyl]-3-methoxybenzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



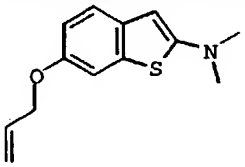
Part A. 4-Allyloxy-α-hydroxy-N,N-dimethylphenyl-thioacetamide.



The title compound was prepared in 70% yield by essentially following the procedure in Example 81, Part A from 4-allyloxybenzaldehyde.

FDMS 251 (M+).

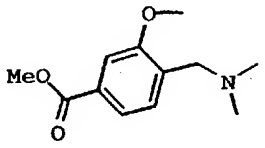
Part B. 6-Allyloxy-2-(dimethylamino)benzo[*b*]thiophene.



The title compound was prepared in 49% yield by essentially following the procedures outlined in Example 81, Part B from the thioacetamide (Part A).

FDMS 233 (M+); Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.76; H, 6.54; N, 5.82.

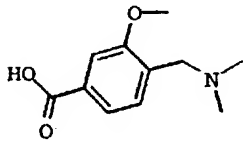
Part C. Methyl 4-(Dimethylamino)methyl-3-methoxybenzoate.



The title compound was prepared in 77% yield by essentially following the procedure outlined in Example 37, Part A from methyl 4-bromomethyl-3-methoxybenzoate (see Example 37, Part A) and dimethylamine.

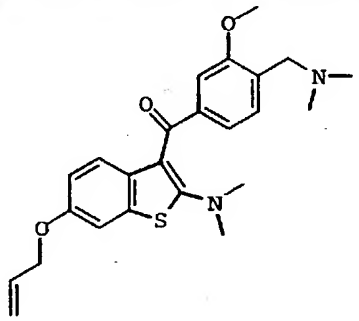
FDMS 223 (M+); Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.52; H, 7.68; N, 6.43.

Part D. 4-(Dimethylamino)methyl-3-methoxybenzoic Acid.



The crude title compound (+30% NaCl by weight) was prepared by essentially following the procedures outlined in Example 20, Part C from the methyl benzoate (Part C).

Part E. 6-Allyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 4-(Dimethylamino)methyl-3-methoxyphenyl Ketone.

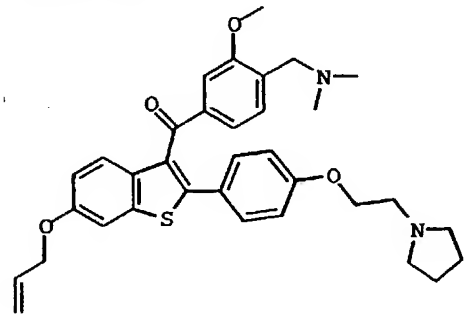


The title compound was prepared in 73% yield (23% SM recovered) by essentially following the procedures outlined in Example 84, Part A from 6-allyloxy-2-(dimethylamino)benzo-

[*b*]thiophene (Part B) and 4-(dimethylamino)methyl-3-methoxybenzoic acid (Part D).

FDMS 424 (M+); Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.90; H, 6.65; N, 6.60. Found: C, 68.18; H, 6.77; N, 6.81.

Part F. 6-Allyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-(Dimethylamino)methyl-3-methoxyphenyl Ketone.



The title compound was prepared in 70% yield by essentially following the procedures outlined in Example 81, Part E from the ketone (Part E) and 4-[2-(1-pyrrolidinyl)-ethoxy]phenyl magnesium bromide (Example 81, Part D).

FDMS 570 (M^+); Anal. Calcd for $C_{34}H_{38}N_2O_4S$: C, 71.55; H, 6.71; N, 4.91. Found: C, 71.30; H, 6.85; N, 4.89.

Part G. 3-[4-(Dimethylamino)methyl-3-methoxybenzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

Deoxygenation of the ketone (Part F) was accomplished in 57% crude yield by essentially following the procedures outlined in Example 21, Part A.

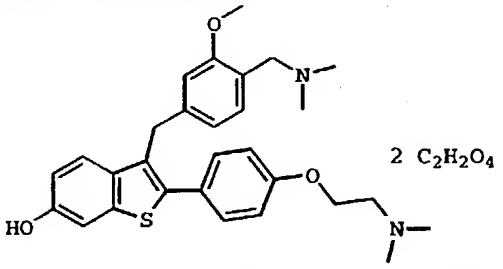
The free base of the title compound was prepared by stirring a slurry of the above crude product (139 mg, .250 mmol), 10% Pd/C (150 mg), and *p*-toluenesulfonic acid monohydrate (105 mg, .551 mmol) in 3 mL of a 5:1 mixture of MeOH-THF solution at reflux for 22 h. The reaction was quenched with 3.5 mL of saturated aqueous $NaHCO_3$ solution,

stirred vigorously for 15 min, and then concentrated to dryness under reduced pressure. The residue was taken up in 200 mL of THF and stirred vigorously for 30 min. The slurry was filtered through a pad of diatomaceous earth and washed with THF. The filtrate was concentrated under reduced pressure and the residue was flash chromatographed (silica gel, 10%[10% NH_4OH in MeOH]/CH_2Cl_2) to afford 66.7 mg (.129 mmol, 52%) of a light brown foam. The title compound was prepared by essentially following the procedures outlined in Example 21, Part C.

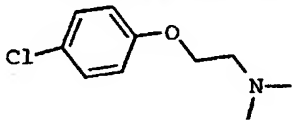
FDMS 517 (M+); Anal. Calcd for $C_{31}H_{36}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 0.7H_2O \cdot 1.2C_4H_8O_2$ (Hygroscopic): C, 58.65; H, 6.31; N, 3.44. Found: C, 58.27; H, 6.31; N, 3.41.

Example 89

Preparation of 2-[4-[2-(Dimethylamino)ethoxy]phenyl]-3-[4-(dimethylamino)methyl-3-methoxybenzyl]-6-hydroxybenzo[*b*]thiophene Dioxalate.



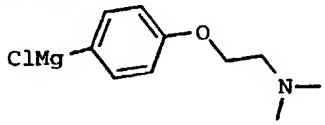
Part A. [2-(4-Chlorophenoxy)ethyl]dimethylamine.



The title compound was prepared in 61% yield (26% SM recovered) by essentially following the procedure outlined in Example 34, Part A from 2-bromoethyl 4-chlorophenyl ether and dimethylamine.

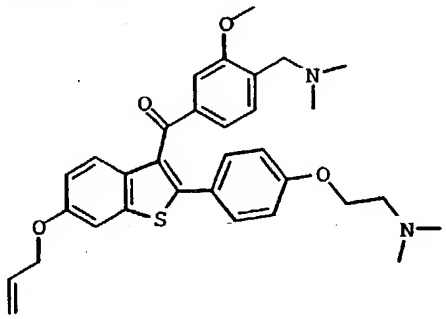
FDMS 199 (M+); Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.01. Found: C, 59.88; H, 7.03; N, 7.22.

Part B. Preparation of 4-[2-(Dimethylamino)ethoxy]-phenyl Magnesium Chloride.



To the chlorobenzene (Part A) in 23.6 mL of freshly distilled THF was added 216 mg of magnesium turnings and a catalytic amount of iodine crystals. The mixture was heated at reflux for 36 h or until all the magnesium was consumed to afford ~23.6 mL of 0.38 M Grignard reagent solution as a milky white suspension.

Part C. 6-Allyloxy-2-[4-[2-(dimethylamino)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-(Dimethylamino)methyl-3-methoxyphenyl Ketone.



The title compound was prepared in 80% yield by essentially following the procedures outlined in Example 81, Part E from the ketone (Example 88, Part E) and the Grignard reagent (Part B).

FDMS 544 (M+); Anal. Calcd for $C_{32}H_{36}N_2O_4S$: C, 70.56; H, 6.66; N, 5.14. Found: C, 70.33; H, 6.73; N, 5.10.

Part D. 2-[4-[2-(Dimethylamino)ethoxy]phenyl]-3-[4-(dimethylamino)methyl-3-methoxybenzyl]-6-hydroxy-benzo[*b*]thiophene Dioxalate.

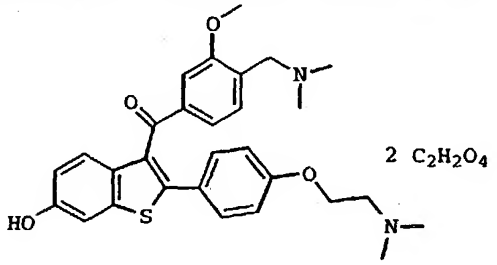
Deoxygenation of the ketone (Part C) was accomplished in 46% by essentially following the procedures outlined in Example 21, Part A.

The free base of the title compound was prepared in 45% yield by essentially following the procedures outlined in Example 88, Part G. The title compound was then prepared by essentially following the procedure outlined in Example 21, Part C.

FDMS 491 (M^+); Anal. Calcd for $C_{29}H_{34}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 1.06C_4H_8O_2$ (Hygroscopic): C, 58.54; H, 6.13; N, 3.67. Found: C, 58.62; H, 6.39; N, 3.79.

Example 90

Preparation of 2-[4-[2-(Dimethylamino)ethoxy]phenyl]-6-hydroxybenzo[*b*]thiophen-3-yl 4-(Dimethylamino)-methyl-3-methoxyphenyl Ketone Dioxalate.

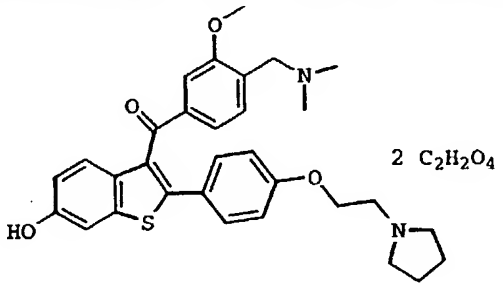


The free base of the title compound was prepared in 37% yield by essentially following the procedures outlined in Example 88, Part G from 6-allyloxy-2-[4-[2-(dimethylamino)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-(dimethylamino)methyl-3-methoxyphenyl ketone (Example 89, Part C). The dioxalate was then prepared by using the procedures from Example 21, Part C from the free base.

FDMS 505 (M+); Anal. Calcd for $C_{29}H_{32}N_2O_4S \cdot 2.0C_2H_2O_4$: C, 57.89; H, 5.30; N, 4.09. Found: C, 57.75; H, 5.47; N, 4.13.

Example 91

Preparation of 4-(Dimethylamino)methyl-3-methoxyphenyl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

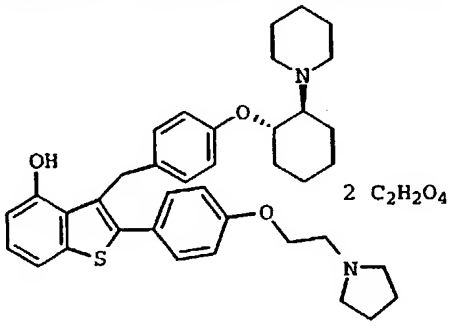


The free base of the title compound was prepared in 81% yield by essentially following the procedures outlined in Example 88, Part G from 6-allyloxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-(dimethylamino)methyl-3-methoxyphenyl ketone (Example 88, Part F). The dioxalate was then prepared by using the procedures from Example 21, Part C from the free base.

FDMS 531 (M+); Anal. Calcd for $C_{31}H_{34}N_2O_4S \cdot 2.0C_2H_2O_4$: C, 59.15; H, 5.39; N, 3.94. Found: C, 58.96; H, 5.73; N, 4.00.

Example 92

Preparation of (±)-4-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. 4-Methoxybenzo[*b*]thiophene and 6-Methoxybenzo[*b*]thiophene.

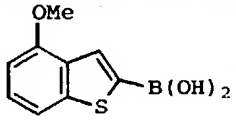
To a mixture of 25.10 g of 3-methoxybenzenethiol and 19.2 mL of bromoacetaldehyde dimethyl acetal in 200 mL of acetone was added 27 g of K_2CO_3 in one portion at room temperature. The white suspension was stirred vigorously at room temperature for 2 h. The mixture was filtered with thorough ethereal rinse. The filtrate was concentrated, taken up in 500 mL of Et_2O, and washed with 300 mL of H_2O, 0.5 N KOH, H_2O, and brine. The washings were back extracted with Et_2O (3 x 500 mL). Combined organic layers were dried over $MgSO_4$ and concentrated to afford 37.46 g (quantitative) of the crude 3-methoxybenzenethioacetaldehyde dimethyl acetal.

To a heated biphasic solution of 53.9 g of PPA in ca. 500 mL of chlorobenzene at 145 °C (bath temp.) was added dropwise 18.44 g of the crude acetal in ca. 100 mL of chlorobenzene over 4.5 h period. The dark green biphasic solution was heated at reflux with vigorous stirring for another 2 h. After cooling to room temperature, the organic layer was separated, concentrated, taken up in 500 mL of EtOAc, and washed with 300 mL of H_2O and brine. The PPA layer was dissolved in ca. 1.0 L of H_2O and extracted with EtOAc (4 x 500 mL). The extracts were washed with 300 mL of H_2O and 1:1 mixture of saturated aqueous $NaHCO_3$ and brine. Combined organic layers were dried over $MgSO_4$, concentrated and purified by PrepLC with hexanes to yield 2.40 g of 4-methoxybenzo[*b*]thiophene and 7.96 g of 6-methoxybenzo[*b*]-thiophene (78% total) which were cleanly separated.

4-methoxybenzothiophene: FDMS 164.0 (M+); Anal. Calcd for C_9H_8OS: C, 65.82; H, 4.91; S, 19.52. Found: C, 66.01; H, 4.90; S, 19.60.

6-methoxybenzothiophene: FDMS 164.0 (M+).

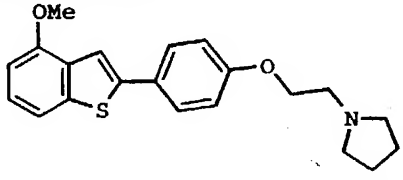
Part B. 4-Methoxybenzo[*b*]thiophene-2-boronic Acid.



The title compound was prepared in 62% yield by essentially following the procedures in Example 1, Part A from 4-methoxybenzothiophene (Part A).

mp 267-270 °C; FDMS 570.

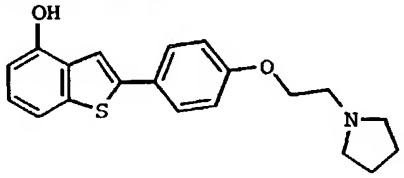
Part C. 4-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 53% yield by essentially following the procedures outlined in Example 1, Part B from 4-methoxybenzo[*b*]thiophene-2-boronic acid (Part B).

FDMS 353 (M^+).

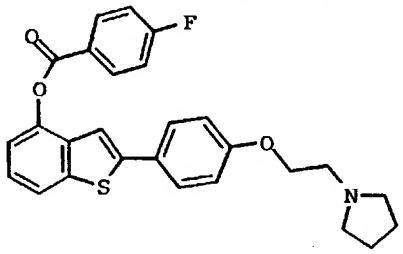
Part D. 4-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared by essentially following the procedures outlined in Example 21, Part B from the methoxybenzo[*b*]thiophene (Part C). Recrystallization from EtOAc-hexanes afforded 712 mg (2.09 mmol, 38%) of off-white needle-like crystals.

mp 191-193 °C; FDMS 339 (M^+); Anal. Calcd for $C_{20}H_{21}NO_2S \cdot 0.17H_2O$: C, 70.13; H, 6.28; N, 4.09. Found: C, 69.81; H, 6.10; N, 3.85.

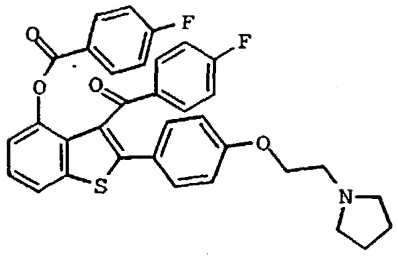
Part E. 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-4-yl 4-Fluorobenzoate.



A mixture of 4-hydroxybenzo[*b*]thiophene (Part D) (607 mg, 1.79 mmol) and 4-fluorobenzoyl chloride (233 µL, 1.97 mmol) in 10 mL of anhydrous dichloroethane was stirred at room temperature for 18 h. Another portion of 4-fluorobenzoyl chloride (166 µL, 1.48 mmol) was added and the reaction mixture was stirred for 3 days. A third portion of acid chloride (233 µl, 1.97 mmol) was added and the mixture was stirred for an additional 4 h. The reaction was then quenched with 25 mL of satd. $NaHCO_3$ soln, and the mixture was extracted (3 x 100 mL) with EtOAc. The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, concentrated under reduced pressure, and flash chromatographed (silica gel, 5%[10% NH_4OH in MeOH]/CH_2Cl_2) to afford 699 mg (1.51 mmol, 85%) of a white solid.

FDMS 461 (M^+); Anal. Calcd for $C_{27}H_{24}FNO_3S \cdot 0.16NH_5O$: C, 69.42; H, 5.35; N, 3.48. Found: C, 69.40; H, 5.30; N, 3.65.

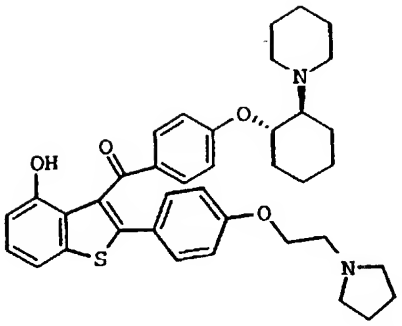
Part F. 3-(4-Fluorophenyl)carbonyl-2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-4-yl 4-Fluorobenzoate.



To a solution of 4-fluorobenzoate (Part E) (683 mg, 1.48 mmol) in 10.0 mL of anhydrous dichloroethane was added 4-fluorobenzoyl chloride (192 µL, 1.63 mmol) at room temperature. The reaction mixture was cooled to 0 °C, and aluminum chloride (789 mg, 5.92 mmol) was added which turned the slurry into a dark red homogeneous solution. The reaction mixture was slowly warmed to room temperature and then stirred for 24 h. Another portion of aluminum chloride (395 mg, 2.94 mmol) and 4-fluorobenzoyl chloride (95 µL, .80 mmol) were added, and the reaction mixture was stirred at room temperature for another 24 h. The reaction mixture was then poured into 25 mL of ice-cold saturated aqueous $NaHCO_3$ solution. The mixture was taken up in EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (4 x 150 mL). The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (MPLC, silica gel, 40:57:3 THF-hexanes-Et_3N) to afford 193 mg (.331 mmol, 22%) of white foam.

mp 58-63 °C; FDMS 583 (M^+); Anal. Calcd for $C_{34}H_{27}F_2NO_4S$: C, 69.97; H, 4.66; N, 2.40. Found: C, 70.37; H, 5.00; N, 2.30.

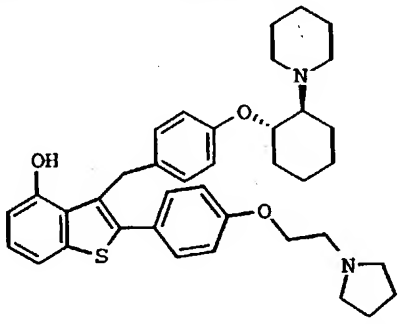
Part G. (±)-4-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 32% yield by essentially following the procedures in Example 75, Part G, from the 4-fluorobenzoate (Part F) and (±)-*trans*-2-(1-piperidyl)cyclohexanol (Example 20, Part A).

FDMS 625 (M+); Anal. Calcd for $C_{38}H_{44}N_2O_4S \cdot 2.5C_2H_2O_4 \cdot 3.2H_2O$: C, 56.91; H,6.15; N, 3.09. Found: C, 56.61; H, 5.80; N, 3.47.

Part H. (±)-4-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene.



The title compound was prepared in 24% yield by essentially following the procedures outlined in Example 21, Part A from the ketone (Part G).

FDMS 610 (M+).

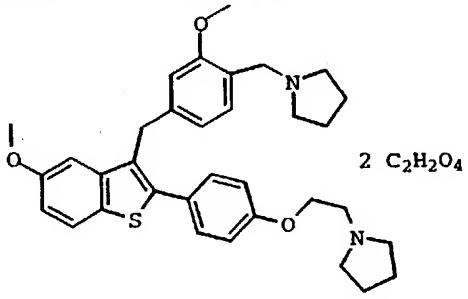
Part I. (±)-4-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared by essentially following the procedure outlined in Example 21, Part C from the free base (Part H).

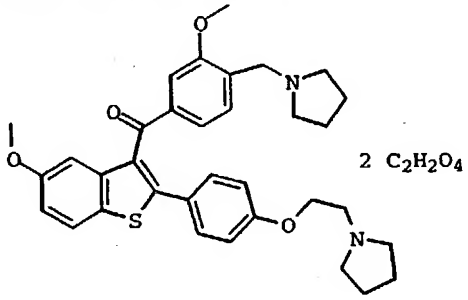
FDMS 611 (M+); Anal. Calcd for $C_{38}H_{46}N_2O_3S \cdot 2.1C_2H_2O_4 \cdot 3.3H_2O$: C, 58.98; H, 6.66; N, 3.26. Found: C, 58.70; H, 6.32; N, 3.28.

Example 93

Preparation of 5-Methoxy-3-[3-methoxy-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. 5-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



The free base of the title compound was prepared in 37% yield by essentially following the procedures outlined in Example 41; Part C from 5-methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene (Example 71, Part C) and 3-methoxy-4-[(1-pyrrolidinyl)methyl]benzoic acid (Example 41, Part B). The title compound was prepared by essentially

following the procedures outlined in Example 21, Part C from the free base.

FDMS 571 (M^+); Anal. Calcd for $C_{34}H_{38}N_2O_4S \cdot 2.0C_2H_2O_4 \cdot 0.48C_4H_8O_2$: C, 60.46; H, 5.83; N, 3.53. Found: C, 60.57; H, 6.08; N, 3.58.

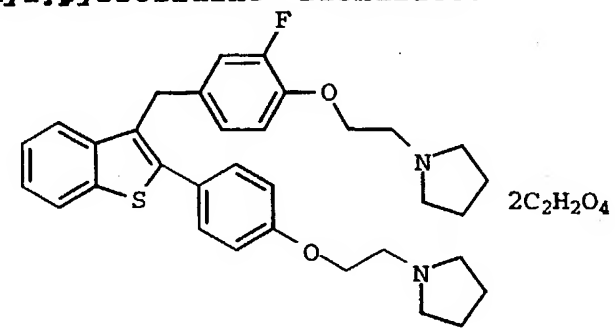
Part B. 5-Methoxy-3-[3-methoxy-4-(1-pyrrolidinyl-methyl)benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

The free base of the title compound was prepared in 68% yield by essentially following the procedures in Example 21, Part A from the free base of ketone (Part A). The title compound was prepared by essentially following the procedures in Example 21, Part C from the free base.

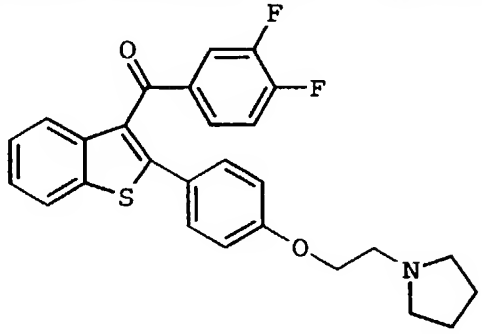
Free base: FDMS 557 (M+); Anal. Calcd for $C_{34}H_{40}N_2O_3S$: C, 73.35; H, 7.24; N, 5.03. Found: C, 73.49; H, 7.12; N, 5.03. Dioxalate: FDMS 557 (M+); Anal. Calcd for $C_{34}H_{40}N_2O_3S \cdot 1.7C_2H_2O_4 \cdot 0.5C_4H_8O_2$: C, 62.77; H, 6.34; N, 3.72. Found: C, 62.63; H, 6.73; N, 3.97.

Example 94

Preparation of 1-[2-[2-Fluoro-4-[[2-[4-[2-(1-pyrro-lidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]-phenoxy]ethyl]pyrrolidine Dioxalate.



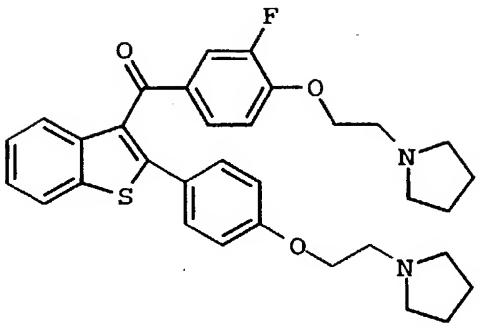
Part A. 3,4-Difluorophenyl 2-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



A slurry of 3.23 g (10 mmol) of 2-[4-[2-(1-pyrrolidinyl)ethoxy)phenyl]benzo[*b*]thiophene in 50 mL of 1,2`dichloroethane was treated with 1.76 g (10 mmol) of 3,4-difluorobenzoyl chloride at 0 °C. The mixture was protected from light and 4.4 mL (40 mmol) $TiCl_4$ was added dropwise. The reaction was stirred at 0 °C for 5 h at which time it was quenched by carefully pouring it into 400 mL of saturated aqueous $NaHCO_3$. To this was added EtOAc (200 mL), and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give a crude oil which was purified by chromatography (SiO_2; 2% MeOH in $CHCl_3$) to afford 1.7 g (3.7 mmol; 37%) of the ketone as a viscous oil.

^1H NMR ($CDCl_3$) δ 7.87-7.75 (m, 2H), 7.63-7.56 (m, 1H), 7.48-7.31 (m, 3H), 7.30-7.25 (m, 2H), 7.03-6.94 (m, 1H), 6.79-6.75 (m, 2H), 4.1 (t, 2H), 2.8 (t, 2H), 2.7-2.5 (m, 4H), 1.84-1.80 (m, 4H); FDMS 463 (M+); Anal. Calcd for $C_{27}H_{23}F_2NO_2S \cdot 1.08CHCl_3$: C, 56.93; H, 4.1; N, 2.36. Found: C, 56.90; H, 4.05; N, 2.45.

Part B. 3-Fluoro-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl Ketone.



A 60% dispersion of sodium hydride in mineral oil (0.39 g, 9.8 mmol) was rinsed with hexanes and dried under reduced pressure. To this was added 30 mL of dry THF, followed by 1.1 g (9.8 mmol) of 1-(2-hydroxyethyl)pyrrolidine. After gas evolution had ceased, a solution of 2.27 g (4.90 mmol) of the 3,4-difluorophenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy)phenyl]-benzo[*b*]thiophen-3-yl ketone in 30 mL of THF was added. The reaction was stirred under a nitrogen atmosphere for 3 h at ambient temperature after which it was poured into a mixture of 100 mL of brine and 60 mL of EtOAc. The layers were separated and the aqueous layer was extracted with 30 mL of EtOAc. The combined organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give 3.2 g of an oil. This was purified twice by chromatrography (SiO_2; 50/45/5% THF/Hex/Et_3N; then 5% $CHCl_3$ in MeOH) to afford 1.6 g (2.9 mmol; 58%) of the desired compound as a viscous oil.

^1H NMR ($CDCl_3$) δ 7.87-7.84 (m, 1H), 7.69-7.66 (m, 1H), 7.58-7.54 (m, 1H), 7.50-7.47 (m, 1H), 7.38-7.26 (m, 3H), 6.81-6.75 (m, 4H), 4.15 (t, 2H), 4.06 (t, 2H), 2.91-2.86 (m, 4H), 2.62-2.61 (m, 8H), 1.82-1.77 (m, 8H); FDMS 461 (M-97), 559 (M+1); Anal. Calcd for $C_{33}H_{35}FN_2O_3S \cdot 1.45CHCl_3$: C, 56.54; H, 5.02; N, 3.83. Found: C, 56.45; H, 5.0; N, 3.87.

100 mg was converted to the dioxalate salt.
Anal. Calcd for $C_{33}H_{35}FN_2O_3S \cdot 2\ C_2H_2O_4 \cdot 1\ H_2O$: C, 58.72; H, 5.46; N, 3.70. Found: C, 58.46; H, 5.06; N, 3.32.

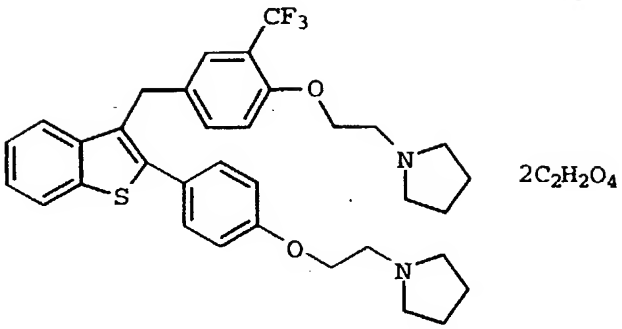
Part C. 1-[2-[2-Fluoro-4-[[2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]-ethyl]pyrrolidine Dioxalate.

A solution of 1.1 g (2 mmol) of 3-fluoro-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy-phenyl]benzo[*b*]thiophen-3-yl ketone in 25 mL of THF at 0 °C was treated with 10 mL of 1 M DIBAL-H in hexanes. The reaction was stirred at 0 °C for 30 min and was quenched by the addition of 5 mL of EtOAc and concentrated *in vacuo*. The resulting residue was immersed in an ice bath, then cautiously treated with 10 mL of TFA, followed by 186 mg (5 mmol) of $NaBH_4$. The reaction was stirred for 2 h, then evaporated *in vacuo*. The residue was taken up in 50 mL of 5 N NaOH and extracted with CH_2Cl_2 (2 X 30 mL). The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to give 900 mg of an oil. Purification by chromatography (MPLC SiO_2; 60/35/5 THF/Hex/TEA) afforded 135 mg (0.25 mmol, 12%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

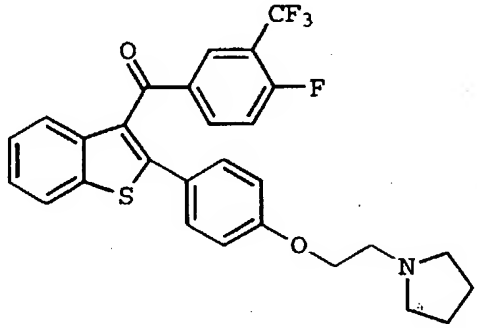
^1H NMR ($CDCl_3$) δ 7.95-7.85 (m, 1H), 7.75-7.7 (m, 1H), 7.6-7.65 (m, 1H), 7.55-7.5 (m, 1H), 7.45-7.38 (m, 4H), 7.05 (s, 1H), 6.85-6.8 (m, 2H), 5.05 (s, 2H), 4.20 (t, 2H), 4.1 (t, 2H), 3.0-2.9 (m, 4H), 2.7-2.6 (m, 8H), 1.8-1.9 (m, 8H); Anal. Calcd for $C_{33}H_{37}FN_2O_2S \cdot 1.65\ C_2H_2O_4$: C, 62.89; H, 5.86; N, 4.04. Found: C, 62.93; H, 6.05; N, 4.00.

Example 95

Preparation of 1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]-2-trifluoromethylphenoxy]ethyl]pyrrolidine Dioxalate.



Part A. 4-Fluoro-3-trifluoromethylphenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



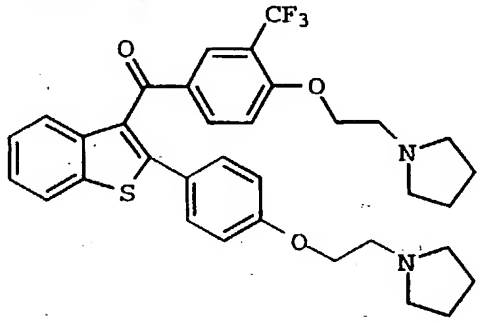
A slurry of 8 g (38.4 mmol) of 4-fluoro-3-trifluoromethyl benzoic acid in 30 mL of dichloromethane and 2 drops of DMF was treated with 6.70 mL (76.9 mmol) of $(COCl)_2$ and the mixture was stirred at ambient temperature for 4 h. The resulting solution was evaporated *in vacuo*, and the residual oil was distilled under reduced pressure to yield 7.2 g (31.8 mmol, 83%) of the acid chloride as a colorless oil.

A solution of 3.38 g (10.45 mmol) of 2-[4-[2-(1-pyrrolidinyl)ethoxy)phenyl]benzo[*b*]thiophene was dissolved in 200 mL of 1,2-dichloroethane and treated with 2.4 g (10.45 mmol) of the above acid chloride at 0 °C. The reaction was protected from light and 4.4 mL (39.8 mmol) $TiCl_4$ was added dropwise. The reaction was stirred at ambient temperature for 4 h at which time it was quenched by carefully pouring it into 500 mL of saturated aqueous $NaHCO_3$. EtOAc (400 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to

give an oil which was purified by chromatography (SiO_2; 78/20/2% Hex/THF/Et_3N) to afford 3.64 g (7.1 mmol; 68%) of the ketone as a solid.

^1H NMR ($CDCl_3$) δ 7.95-7.85 (m, 3H), 7.45-7.35 (m, 3H), 7.30-7.2 (m, 2H), 7.1-7.00 (m, 1H), 6.79-6.72 (m, 2H), 4.05 (t, 2H), 2.85 (t, 2H), 2.7-2.5 (m, 4H), 1.85-1.75 (m, 4H); FDMS 514 (M+1); Anal. Calcd for $C_{28}H_{23}F_4NO_2S$: C, 65.89; H, 4.51; N, 2.73. Found: C, 65.75; H, 4.68; N, 2.78.

Part B. 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]-benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]-3-trifluorophenyl Ketone.



A 60% dispersion of sodium hydride in mineral oil (0.47 g, 11.7 mmol) was rinsed with hexanes and dried under reduced pressure. To this was added 25 mL of dry DMF followed by 1.35 g (11.7 mmol) 1-(2-hydroxyethyl)pyrrolidine. After gas evolution had ceased, a solution of 3 g (5.8 mmol) of 4-fluoro-3-trifluoromethylphenyl 2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone in 30 mL of DMF was added. The reaction was stirred under a nitrogen atmosphere overnight at ambient temperature, after which it was poured into a mixture of 100 mL of brine and 60 mL of EtOAc. The layers were separated and the aqueous layer was extracted with 30 mL of EtOAc. The combined organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to 3.8 g of an oil. This was purified by chromatrography (SiO_2; 5% MeOH/1% NH_4OH in

$CHCl_3$) to afford 3.07 g (5 mmol; 87%) of the named compound as a viscous oil.

FDMS 609 (M+1)

412 mg was converted to the dioxalate salt.
^1H NMR (DMSO-d_6) δ 8.1 (d, 1H), 8.0-7.9 (m, 2H), 7.65 (d, 1H), 7.5-7.4 (m, 2H), 7.4-7.3 (m, 2H), 7.15 (d, 1H), 6.9-7.0 (d, 2H), 4.55 (bs, 4H), 4.55-4.4 (m, 2H), 4.2-4.3 (m, 2H), 3.4-3.6 (m, 4H); 3.1-3.3 (m, 8H), 1.8-1.95 (m, 8H); Anal. Calcd for $C_{34}H_{35}F_3N_2O_3S \cdot 1.5C_2H_2O_4$: C, 59.75; H, 5.15; N, 3.77. Found: C, 59.61; H, 5.16; N, 3.80.

Part C. 1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl]methyl]-2-trifluoro-methylphenoxy]ethyl]pyrrolidine Dioxalate.

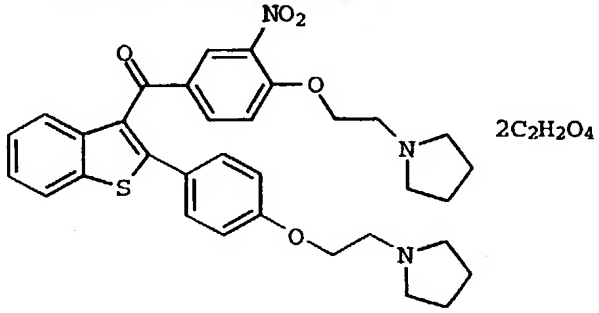
A solution of 1 g (1.64 mmol) of the 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]-3-trifluorophenyl ketone in 30 mL of THF at 0 °C was treated with 9 mL of 1 M DIBAL-H in hexanes. The reaction was stirred at 0 °C for 1 h and was quenched by the addition of 5 mL of EtOAc and concentrated *in vacuo*. The resulting residue was immersed in an ice bath then cauiously treated with 10 mL of TFA followed by 124 mg (3.30 mmol) of $NaBH_4$. The reaction was stirred for 2 h then evaporated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ (25 mL) and $CHCl_3$ (50 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 X 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give 1.1 g of an oil. Purification by chromatography (SiO_2; 2% MeOH in $CHCl_3$) afforded 353 mg (0.59 mmol 36%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

^1H NMR (Free Base-$CDCl_3$) δ 7.84-7.81 (m, 1H), 7.48-7.45 (m, 1H), 7.4-7.31 (m, 3H), 7.31-7.15 (m, 2H), 7.15-7.11 (m, 1H),

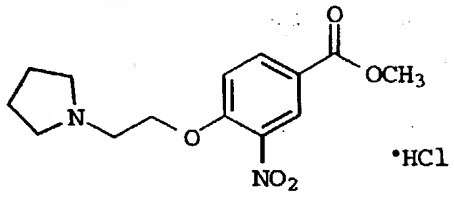
6.93-6.98 (m, 2H), 6.82 (d, 1H), 4.2 (s, 2H), 4.15-4.1 (m, 4H), 2.95 (t, 4H); 2.65-2.55 (m, 8H), 1.85-1.75 (m, 8H); Anal. Calcd for $C_{38}H_{41}F_3N_2O_{10}S$: C, 58.91; H, 5.33; N, 3.62. Found: C, 58.80; H, 5.27; N, 3.57.

Example 96

Preparation of 3-Nitro-4-[2-(1-pyrrolidinyl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]-thiophen-3-yl Ketone Dioxalate.



Part A. Methyl 3-Nitro-4-[2-(1-pyrrolidinyl)ethoxy]-benzoate Hydrochloride.

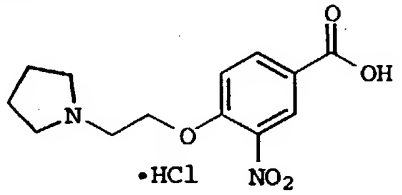


A mixture of 32 g (162.4 mmol) of methyl 4-hydroxy-3-nitrobenzoate, 51.13 g (194.9 mmol) of triphenylphosphine, 22.45 g (194.9 mmol) of 1-(2-hydroxyethylpyrrolidine), and 600 mL of CH_2Cl_2 was cooled to 0 °C and treated with 33.95 g of (194.9 mmol) diethyl azodicarboxylate. The cooling bath was removed and the reaction was stirred at ambient temperature for 16 h. It was concentrated to dryness under reduced pressure, mixed with 200 mL of $CHCl_3$ and filtered. The filtrate was chromatographed (SiO_2; 3% MeOH in $CHCl_3$) to give 14.63 g of product still contaminated with methyl 4-hydroxy-3-nitrobenzoate. It was dissolved in 200 mL of EtOAc and treated with HCl gas for 2 min. The resulting

solid was filtered to yield 11.81 g (36 mmol, 22%) of the HCl salt of the named product.

^1H NMR (DMSO-d_6) δ 10.85-11 (bs, 1H), 8.45 (d, 1H), 8.25 (dd, 1H), 7.58 (d, 1H), 4.65 (t, 2H), 3.9 (s, 3H), 3.7-3.55 (m, 4H), 3.05-3.4 (m, 2H); 2.1-1.8 (m, 4H); FDMS 294 (M+); Anal. Calcd for $C_{14}H_{18}N_2O_5 \cdot HCl$: C, 50.84; H, 5.79; N, 8.47. Found: C, 50.84; H, 5.70; N, 8.62.

Part B. 3-Nitro-4-[2-(1-pyrrolidinyl)ethoxy]benzoic Acid Hydrochloride.



Methyl 3-nitro-4-[2-(1-pyrrolidinyl)ethoxy]benzoate (5.9 g, 20 mmol) was mixed with 60 mL of 5 N aqueous HCl and refluxed 16 h. It was mixed with toluene/EtOH and concentrated under reduced pressure to dryness. The resulting solid was tritrated with hot EtOAc to afford 5.7 g (18 mmol, 90%) of the benzoic acid hydrochloride.

^1H NMR (DMSO-d_6) δ 8.36 (d, 1H), 8.22(dd, 1H), 7.45 (d, 1H), 4.21 (t, 2H), 3.65-3.4 (m, 5H), 3.0-3.2 (m, 3H), 2.1-1.7 (m, 4H); FDMS 280 (M+); Anal. Calcd for $C_{13}H_{16}N_2O_5 \cdot HCl \cdot 0.11$toluene: C, 50.60; H, 5.50; N, 8.47. Found: C, 50.60; H, 5.51; N, 8.57.

Part C. 3-Nitro-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

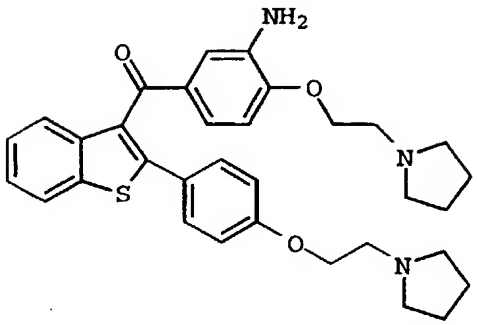
A mixture of 2 g (6.3 mmol) of 3-nitro-4-[2-(1-pyrrolidinyl)ethoxy]benzoic acid hydrochloride, 20 mL of $SOCl_2$, 50 mL of 1,2-dichloroethane and 2 drops of DMF was heated at reflux for 16 h then evaporated *in vacuo* to dryness. The resulting solid was dissolved in 50 mL of 1,2-dichloroethane

and concentrated under reduced pressure. It was redissolved in 50 mL of 1,2-dichloroethane and treated sequentially with a solution of 2 g (6.2 mmol) of 2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene in 150 mL of 1,2-dichloroethane and 3.3 g (24.7 mmol) of $AlCl_3$ at 0 °C. The reaction was protected from light and stirred at 0 °C for 5 h at which time it was quenched by carefully pouring it into 200 mL of vigorously stirred saturated aqueous $NaHCO_3$. A solution of 200 mL of EtOAc and 400 mL of THF was added and the mixture was filtered through diatomaceous earth and the two layers were separated. The aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give an oil which was purified by chromatography (SiO_2; 10% MeOH in $CHCl_3$) to afford 1.26 g (2.2 mmol; 36%) of the desired compound as an oil. A sample of 200 mg was converted to the dioxalate salt according to the method of Example 1, Part C.

^1H NMR (Free Base-$CDCl_3$) δ 8.17 (d, 1H), 7.93 (dd, 1H), 7.87 (dd, 1H), 7.81-7.78 (m, 1H), 7.41-7.38 (m, 2H), 7.31-7.27 (m, 2H), 6.93 (d, 1H), 6.78-6.75 (m, 2H), 4.22 (t, 2H), 4.04 (t, 2H), 2.92 (t, 2H), 2.86 (t, 2H), 2.61-2.58 (m, 8H), 1.81-1.76 (m, 8H); FDMS 586 (M+1); Anal. Calcd for $C_{33}H_{35}N_3O_5S \cdot 2C_2H_2O_4$: C, 58.03; H, 5.13; N, 5.49. Found: C, 58.30; H, 5.13; N, 5.74.

Example 97

Preparation of 3-Amino-4-[2-(1-pyrrolidinyl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]-benzo[*b*]thiophen-3-yl Ketone Dioxalate.



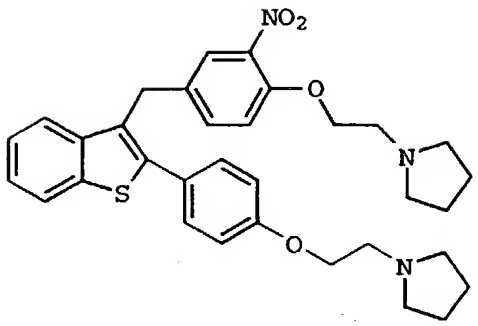
$2C_2H_2O_4$

A solution of 3-nitro-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone (0.57 g 1 mmol) in 10 mL of EtOH and 10 mL of HOAc was hydrogenated in a shaken hydrogenation apparatus for 60 h with 0.5 g of 5% Pd/C and an initial hydrogen pressure of 4.1 bar. The mixture was filtered through diatomaceous earth and concentrated under reduced pressure to an oil. This was partitioned between 10 mL of saturated aqueous $NaHCO_3$ and a 70/30 mixture of EtOAc and MeOH. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to an oil which was purified by chromatrography (SiO_2; 5% MeOH/1% NH_4OH in $CHCl_3$) to afford 0.26 g (0.47 mmol; 47%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

^1H NMR (Free Base-$CDCl_3$) δ 7.82-7.79 (m, 1H), 7.57-7.55 (m, 1H), 7.37-7.30 (m, 2H), 7.29-7.26 (m, 3H), 7.12-7.08 (m, 1H), 6.78-6.75 (m, 2H), 6.58 (d, 1H), 4.07 (t, 2H), 4.04 (t, 2H), 4.00 (bs, 2H), 2.88-2.81 (m, 4H), 2.59-2.55 (m, 8H), 1.79-1.74 (m, 8H); FDMS 556 (M+1); Anal. Calcd for $C_{33}H_{37}N_3O_3S \cdot 0.6C_2H_2O_4 \cdot 1.8$ MeOH: C, 56.69; H, 5.87; N, 4.95. Found: C, 55.98; H, 5.88; N, 5.24

Example 98

Preparation of 1-[2-[2-Nitro-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



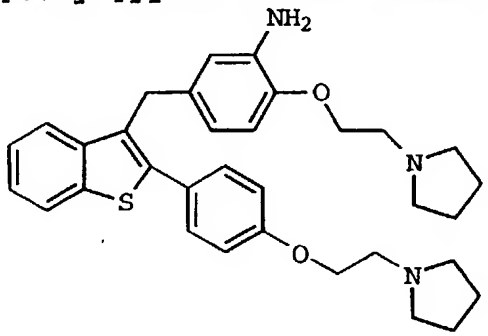
$2C_2H_2O_4$

A solution of 5.7 g (9.7 mmol) of 3-nitro-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy-phenyl]benzo[*b*]thiophen-3-yl ketone in 200 mL of CH_2Cl_2 at 0 °C was treated with 49 mL of 1 M DIBAL-H in hexanes. The reaction was stirred at 0 °C for 1 h then concentrated *in vacuo* to an oil. The resulting residue was immersed in an ice bath then cautiously treated with 25 mL of TFA dropwise, followed by 736 mg (19.5 mmol) of $NaBH_4$. The reaction was stirred for 30 min then evaporated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ (25 mL) and EtOAc (300 mL). Aqueous 5 N NaOH (50 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 X 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give 8 g of an oil. Purification by chromatography (SiO_2; 2% MeOH in $CHCl_3$) afforded 3.1 g (5.4 mmol 56%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

^1H NMR (Free Base-$CDCl_3$) δ 7.85-7.82 (m, 1H), 7.62 (d, 1H), 7.46-7.43 (m, 1H), 7.38-7.29 (m, 4H), 7.20 (dd, 1H), 6.97-6.91 (m, 3H), 4.22 (s, 2H), 4.19-4.12 (m, 4H), 2.92 (t, 4H), 2.65-2.60 (m, 8H), 1.84-1.76 (m, 8H); FDMS 572 (M+1); Anal. Calcd for $C_{33}H_{37}N_3O_4S \cdot 2C_2H_2O_4$: C, 59.11; H, 5.50; N, 5.59. Found: C, 59.40; H, 5.46; N, 5.87

Example 99

Preparation of 1-[2-[2-Amino-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



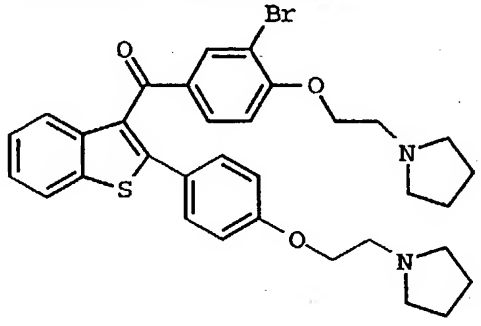
$2C_2H_2O_4$

The title compound was prepared in 36% yield from 1-[2-[2-nitro-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl]methyl]phenoxy]ethyl]pyrrolidine by essentially following the procedure detailed for the preparation of Example 97.

Anal. Calcd for $C_{33}H_{39}N_3O_2S \cdot 2C_2H_2O_4 \cdot 0.95$ MeOH: C, 60.59; H, 6.27; N, 5.59. Found: C, 60.62; H, 6.12; N, 5.30

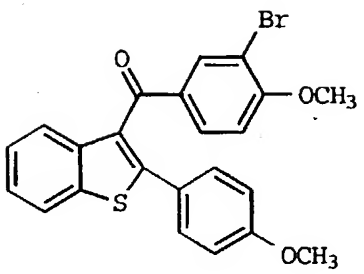
Example 100

Preparation of 3-Bromo-4-[2-(1-pyrrolidinyl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]-thiophen-3-yl Ketone Dioxalate.



$2C_2H_2O_4$

Part A. 3-Bromo-4-methoxyphenyl 2-(4-Methoxyphenyl)-benzo[*b*]thiophen-3-yl Ketone.

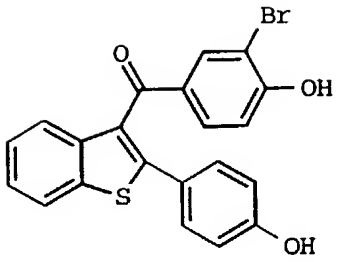


A slurry of 13.35 g (58 mmol) of 3-bromo-4-methoxybenzoic acid in 120 mL of 1,2-dichloroethane and 1 mL of DMF was treated with 8.4 mL (116 mmol) of $SOCl_2$ and the mixture was heated at reflux for 16 h. The resulting solution was evaporated *in vacuo* to an oil which was mixed with 50 mL of 1,2-dichloroethane and reconcentrated under reduced pessure.

A solution of the above oil in 120 mL of 1,2-dichloroethane was treated with 13.86 g (58 mmol) of 2-[4-methoxy)-phenyl]benzo[*b*]thiophene. The mixture was cooled to 0 °C, protected from light and treated with 25 mL (228 mmol) of $TiCl_4$ dropwise. The reaction was stirred at 0 °C for 3 h at which time it was quenched by the careful addition of 100 mL of saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$. It was dried over Na_2SO_4 and evaporated *in vacuo* to give 28 g of a solid which was purified by chromatography (SiO_2; 50% $CHCl_3$ in Hex) to afford 17.13 g (37.81 mmol; 65%) of the ketone as a solid.

^1H NMR ($CDCl_3$) δ 8.03 (d, 1H), 7.88-7.85 (m, 1H), 7.72-7.67 (m, 2H), 7.38-7.33 (m, 4H), 6.81-6.71 (m, 3H), 3.88 (s, 3H), 3.76 (s, 3H).

Part B. 3-Bromo-4-hydroxyphenyl 2-(4-Hydroxyphenyl)-benzo[*b*]thiophen-3-yl Ketone.



A 0 °C solution of 6.5 g (14.3 mmol) of 3-bromo-4-methoxyphenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone in 300 mL of dichloromethane was treated with 15.3 g (115 mmol) of $AlCl_3$, followed by 17 mL (230 mmol) of ethanethiol. The cold bath was removed and the reaction was stirred at ambient temperature for 3.5 h. The reaction mixture was cooled to 0 °C and poured into cold water. The layers were separated and the aqueous layer was extracted with EtOAc (2 X 150 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 5.9 g (13.9 mmol, 97%) of an oil which crystallized out when mixed with CH_2Cl_2.

^1H NMR (DMSO-d_6) δ 11.4 (bs, 2H), 8.1-8.05 (m, 1H), 7.8 (d, 1H), 7.62-7.5 (m, 2H), 7.45-7.35 (m, 2H), 7.25 (d, 2H), 6.85 (d, 1H), 6.75 (d, 2H); FDMS 425.8 (M+1).

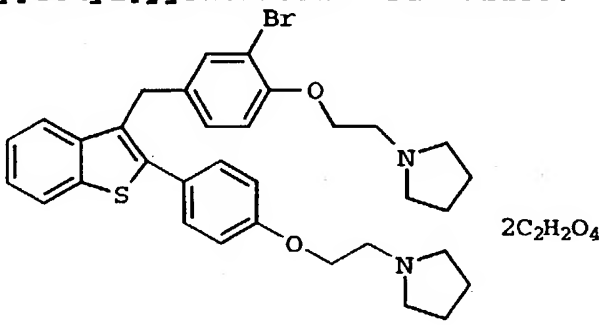
Part C. 3-Bromo-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

A solution of 1 g (2.4 mmol) of the above bis-hydroxybenzothiophene in 25 mL of DMF was treated with 1.6 g (9.6 mmol) of 1-(2-chloroethyl)pyrrolidine hydrochloride followed by 4.7 g (14.4 mmol) of Cs_2CO_3. The mixture was heated to 85 °C for 16 h at which time it was cooled and poured into 100 mL of brine and extracted with EtOAc (3 X 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give 1.1 g of an oil which was purified by radial chromatography (SiO_2; 60:35:5 hexanes-THF-TEA) to afford 0.68 g (1.1 mmol; 46%) of an oil. The oil was converted to the dioxalate salt according to the method of Example 1, Part C.

^{1}H NMR (Free Base-$CDCl_3$) δ 8.31 (d, 1H), 7.84 (dd, 1H), 7.71-7.68 (m, 1H), 7.65 (dd, 1H), 7.38-7.32 (m, 3H), 6.98 (s, 1H), 6.8-6.77 (m, 2H), 6.69 (d, 1H),4.13 (t, 2H), 4.05 (t, 2H), 2.93 (t, 2H), 2.86 (t, 2H), 2.67-2.57 (m, 8H), 1.81-1.76 (m, 8H); FDMS 619 (M+).

Example 101

Preparation of 1-[2-[2-Bromo-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



To a solution of 83 mg (2.20 mmol) of LAH in 20 mL of dry THF was added dropwise a solution of 0.68 g (1.1 mmol) of 3-bromo-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone in 15 mL of dry THF at 0 °C. The reaction was stirred at ambient temperature for 2 h then quenched with 5 mL of EtOAc and poured into 100 mL of brine. The mixture was extracted with 150 mL of 20% MeoH in EtOAc. The extracts were dried over $MgSO_4$ and concentrated to 537 mg of an oil.

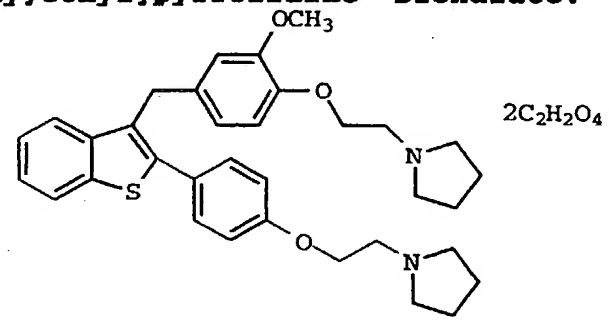
The resulting oil was mixed with 10 mL of TFA, cooled to 0 °C and treated with 65 mg (1.73 mmol) of $NaBH_4$. The cooling bath was removed and the reaction was stirred for 16 h. It was evaporated *in vacuo* and partitioned between saturated aqueous $NaHCO_3$ (25 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to give 450 mg of an oil. Purification by chromatography (SiO_2; 1% MeOH/0.5%

NH_4OH in $CHCl_3$) afforded 122 mg (0.2 mmol 23%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

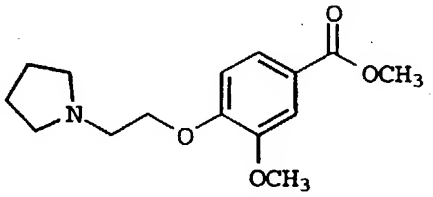
FDMS 605 (M+).

Example 102

Preparation of 1-[2-[2-Methoxy-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



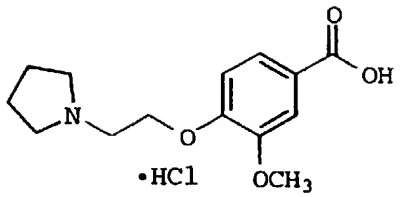
Part A. Methyl 3-Methoxy-4-[2-(1-pyrrolidinyl)-ethoxy]benzoate.



The substituted pyrrolidine was prepared in 94% yield from methyl 4-hydroxy-3-methoxybenzoate and K_2CO_3 by essentially following the procedure detailed for the preparation of Example 100, Part C.

^1H NMR ($CDCl_3$) δ 7.63 (d, 1H), 7.53 (s, 1H), 6.9 (d, 1H), 4.2 (t, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.96 (t, 2H), 2.64-2.61 (m, 4H), 1.85-1.75 (m, 4H); FDMS 279 (M+).

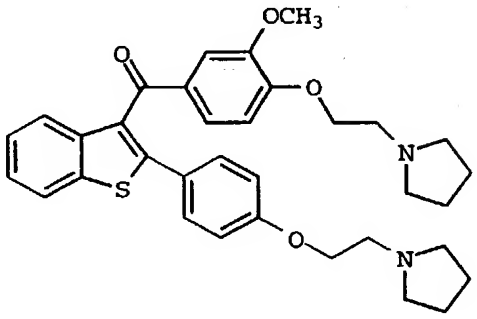
Part B. 3-Methoxy-4-[2-(1-pyrrolidinyl)ethoxy]benzoic Acid Hydrochloride.



The benzoic acid hydrochloride was prepared in 63% yield from methyl 3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]benzoate by essentially following the procedure detailed for the preparation of Example 96, Part B.

^{1}H NMR (DMSO-d_6) δ 11.27 (bs, 2H), 7.57 (d, 1H), 7.55 (s, 1H), 7.12 (d, 1H), 4.44 (t, 2H), 3.82 (s, 3H), 3.5 (bs, 4H), 3.1 (bs, 2H); 1.98 (bs, 2H), 1.89 (bs, 2H); Anal. Calcd for $C_{14}H_{19}NO_4 \cdot HCl$: C, 55.72; H, 6.68; N, 4.64. Found: C, 56.01; H, 6.88; N, 4.70.

Part C. 3-Methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenylbenzo[*b*]thiophen-3-yl Ketone.



The ketone was prepared in 33% yield from 3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]benzoic acid hydrochloride by essentially following the procedure detailed for the preparation of Example 96, Part C.

^{1}H NMR (Free Base-$CDCl_3$) δ 7.86-7.83 (m, 1H), 7.67-7.64 (m, 1H), 7.49 (d, 1H), 7.38-7.26 (m, 5H), 6.8-6.76 (m, 2H), 6.67 (d, 1H), 4.12 (t, 2H), 4.06 (t, 2H), 3.83 (t, 3H), 2.94 (t,

2H), 2.88 (t, 2H), 2.62-2.58 (m, 8H), 1.81-1.76 (m, 8H); FDMS 570 (M+).

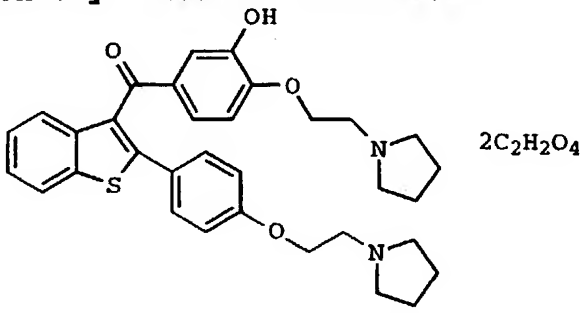
Part D. 1-[2-[2-Methoxy-4-[[2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]-ethyl]pyrrolidine Dioxalate.

The title compound was prepared in 10% yield from 3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 101.

^{1}H NMR (Free Base-$CDCl_3$) δ 7.98-795 (m, 1H), 7.64-761 (m, 1H), 7.50 (d, 2H), 7.36-7.33 (m, 2H), 7.12 (d, 2H), 6.87-6.84 (m, 2H), 6.51 (d, 1H), 6.2 (bs, 4H), 4.34 (t, 2H), 4.20 (s, 2H), 4.16 (t, 2H), 3.68 (s, 3H), 3.5 (t, 2H), 2.86 (t, 2H), 2.67-2.57 (m, 8H), 2.0-1.9 (m, 8H); FDMS 557 (M+1); Anal. Calcd for $C_{34}H_{40}N_2O_3S \cdot 2C_2H_2O_4$: C, 61.94; H, 6.02; N, 3.80. Found: C, 62.23; H, 6.09; N, 3.89.

Example 103

Preparation of 3-Hydroxy-4-[2-(1-pyrrolidinyl)-ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]-benzo[*b*]thiophen-3-yl Ketone Dioxalate.

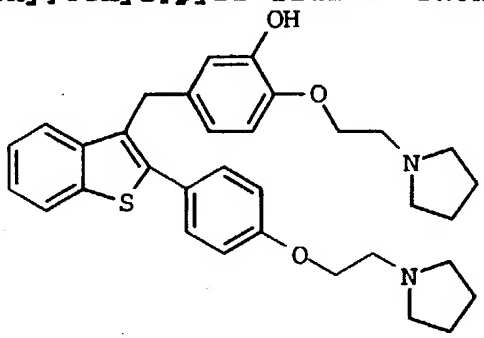


The title compound was prepared in 83% yield from 3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 100, Part B.

Anal. Calcd for $C_{33}H_{36}N_2O_4S \cdot 2C_2H_2O_4 \cdot 1.25H_2O$: C, 58.53; H, 5.64; N, 3.69. Found: C, 58.42; H, 5.27; N, 3.86.

Example 104

Preparation of 1-[2-[2-Hydroxy-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



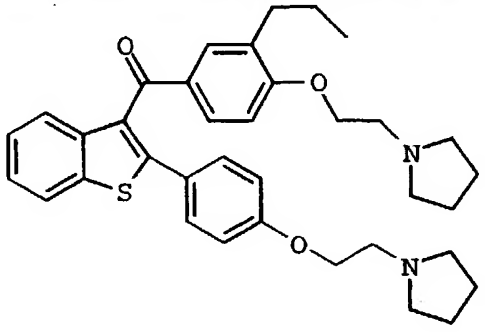
$2C_2H_2O_4$

The title compound was prepared in 29% yield from 3-hydroxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 95, Part C.

FDMS 541.9; Anal. Calcd for $C_{33}H_{38}N_2O_3S \cdot 1.75C_2H_2O_4$: C, 62.6; H, 5.97; N, 4.00. Found: C, 62.44; H, 6.09; N, 4.11.

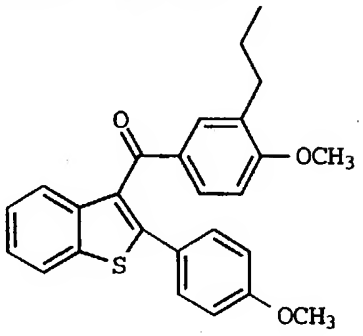
Example 105

Preparation of 3-Propyl-4-[2-(1-pyrrolidinyl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]-benzo[*b*]thiophen-3-yl Ketone Dioxalate.



$2C_2H_2O_4$

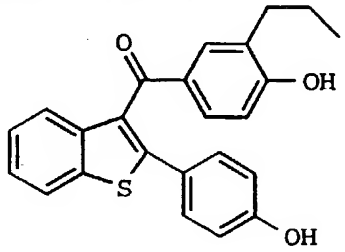
Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-Methoxy-3-propylphenyl Ketone.



A mixture of 3-bromo-4-methoxyphenyl 2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl ketone (1 g, 2.2 mmol), tetrapropyltin (1.6 g, 5.5 mmol), tetrakis(triphenylphosphine)palladium(0) (150 mg, 0.13 mmol) and toluene (20 mL) was heated in a sealed tube at 130 °C for 18 h. The mixture was concentrated under reduced pressure, mixed with 30 mL of diethyl ether and stirred vigorously with 30 mL saturated aqueous KF for 2 h. The layers were separated and the organic layer was dried over $MgSO_4$ then concentrated to dryness. Purification by chromatography (SiO_2; 45% $ClCH_2CH_2Cl$ in Hex) afforded 0.88 g (2.1 mmol 96%) of the propyl compound as a solid.

FDMS 416 (M+); Anal. Calcd for $C_{26}H_{24}O_3S \cdot H_2O$: C, 71.86; H, 6.03. Found: C, 71.46; H, 5.82.

Part B. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-Hydroxy-3-propylphenyl Ketone.



The named compound was prepared in quanitative yield from 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-methoxy-3-propyl-

phenyl ketone by essentially following the procedure detailed for the preparation of Example 100, Part B.

FDMS 388 (M+); Anal. Calcd for $C_{24}H_{20}O_3S \cdot 0.72CHCl_3$: C, 62.69; H, 4.44. Found: C, 62.58; H, 4.4.

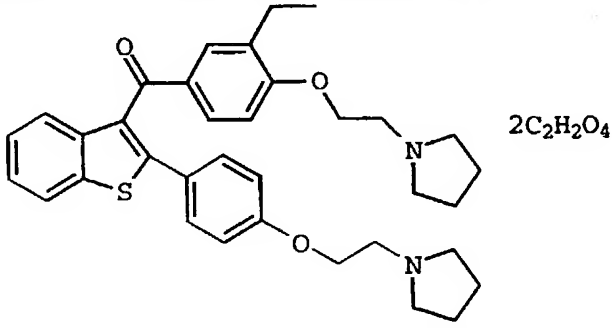
Part C. 3-Propyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

The title compound was prepared in 69% yield from 3-propyl-4-hydroxyphenyl 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 100, Part C.

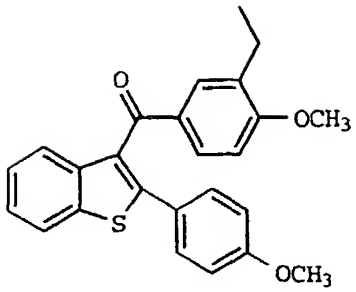
^1H NMR (Free base-$CDCl_3$) δ 7.86-7.83 (m, 1H), 7.67-7.58 (m, 3H), 7.38-7.32 (m, 4H), 6.79-6.76 (m, 2H), 6.66 (d, 1H), 4.09 (t, 2H), 4.03 (t, 2H), 2.89 (t, 2H), 2.85 (t, 2H), 2.62-2.59 (m, 8H), 2.51-2.46 (m, 2H), 1.79-1.65 (m, 8H), 1.52-1.44 (m, 2H), 0.84 (t, 3H); FDMS 583 (M+1); Anal. Calcd for $C_{36}H_{42}N_2O_3S \cdot 2C_2H_2O_4 \cdot 0.15CCl_4$: C, 71.66; H, 6.99; N, 4.62. Found: C, 71.85; N, 7.23; N, 4.23.

Example 106

Preparation of 3-Ethyl-4-[2-(1-pyrrolidinyl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]-benzo[*b*]thiophen-3-yl Ketone Dioxalate.



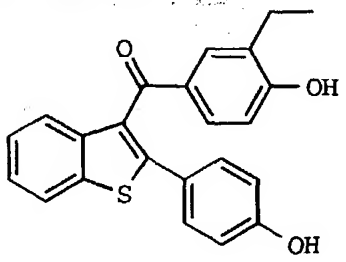
Part A. 3-Ethyl-4-methoxyphenyl 2-(4-Methoxyphenyl)-benzo[*b*]thiophen-3-yl Ketone.



The ethyl compound was prepared in 45% yield from 3-bromo-4-methoxyphenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone and tetraethyltin by essentially following the procedure detailed for the preparation of Example 105, Part A.

Anal. Calcd for $C_{25}H_{22}O_3S$: C, 74.6; H, 5.51. Found: C, 74.9; N, 5.65.

Part B. 3-Ethyl-4-hydroxyphenyl 2-(4-Hydroxyphenyl)-benzo[*b*]thiophen-3-yl Ketone.



The named compound was prepared in 96% yield from 3-ethyl-4-methoxyphenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 100, Part B.

FDMS 374 (M+); Anal. Calcd for $C_{23}H_{18}O_3S \cdot 0.1CHCl_3$: C, 71.81; H, 4.72. Found: C, 71.92; N, 4.81.

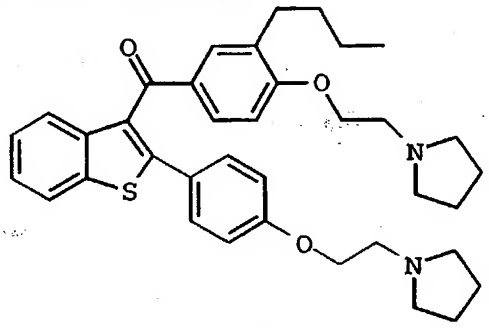
Part C. 3-Ethyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

The title compound was prepared in 42% yield from 3-ethyl-4-hydroxyphenyl 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 100, Part C.

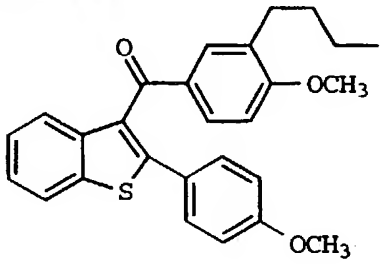
^{1}H NMR (Free base-$CDCl_3$) δ 7.91-7.88 (m, 1H), 7.73-7.62 (m, 3H), 7.43-7.35 (m, 4H), 6.82 (d, 2H), 6.71 (d, 1H), 4.15 (t, 2H), 4.09 (t, 2H), 2.95 (t, 2H), 2.90 (t, 2H), 2.67-2.55 (m, 10H), 1.9-1.84 (m, 8H), 1.13 (t, 3H); FDMS 569 (M+1); Anal. Calcd for $C_{35}H_{40}N_2O_3S \cdot 2C_2H_2O_4$: C, 62.55; H, 5.92; N, 3.74. Found: C, 62.33; H, 5.85; N, 3.74.

Example 107

Preparation of 3-Butyl-4-[2-(1-pyrrolidinyl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]-benzo[*b*]thiophen-3-yl Ketone.



Part A. 3-Butyl-4-methoxyphenyl 2-(4-Methoxyphenyl)-benzo[*b*]thiophen-3-yl Ketone.

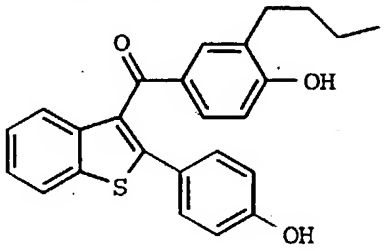


The butyl compound was prepared in 49% yield from 3-bromo-4-methoxyphenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone and tetrabutyltin by essentially following the

procedure detailed for the preparation of Example 105, Part A.

FDMS 430 (M+); Anal. Calcd for $C_{27}H_{26}O_3S \cdot 0.25H_2O$: C, 74.54; H, 6.14. Found: C, 74.79; N, 6.32.

Part B. 3-Butyl-4-hydroxyphenyl 2-(4-Hydroxyphenyl)-benzo[*b*]thiophen-3-yl Ketone.



The named compound was prepared in 98% yield from of 3-butyl-4-methoxyphenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 100, Part B.

Anal. Calcd for $C_{25}H_{22}O_3S \cdot 0.5CHCl_3$: C, 66.27; H, 4.91. Found: C, 66.29; N, 4.84.

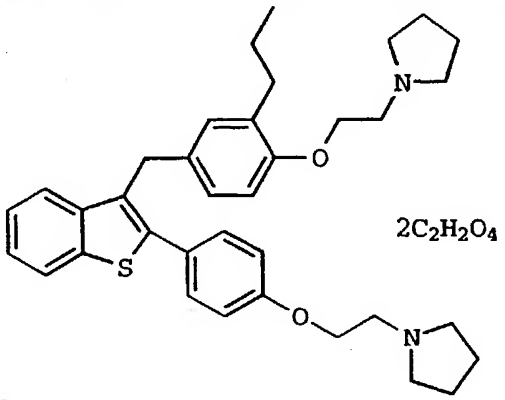
Part C. 3-Butyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl Ketone.

The title compound was prepared in 49% yield from 3-butyl-4-hydroxyphenyl 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 100, Part C.

^1H NMR (Free base-$CDCl_3$) δ 7.86-7.83 (m, 1H), 7.67-7.58 (m, 3H), 7.38-7.32 (m, 4H), 6.79-6.76 (m, 2H), 6.66 (d, 1H), 4.09 (t, 2H), 4.03 (t, 2H), 2.89 (t, 2H), 2.85 (t, 2H), 2.62-2.56 (m, 8H), 2.50 (t, 2H), 1.94-1.78 (m, 8H), 1.46-1.38 (m, 2H), 1.28-1.2 (m, 2H), 0.88 (t, 3H); FDMS 597 (M+1); Anal. Calcd for $C_{37}H_{44}N_2O_3S \cdot 0.7Hex$: C, 75.3; H, 8.25; N, 4.26. Found: C, 75.24; H, 7.90; N, 3.87.

Example 108

Preparation of 1-[2-[2-Propyl-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

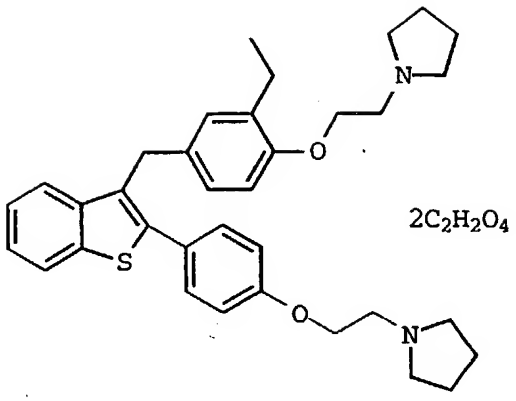


The title compound was prepared in 56% yield from 3-propyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 101.

^1H NMR (Free base-$CDCl_3$) δ 7.84-7.81 (m, 1H), 7.54-7.51 (m, 1H), 7.44-7.42 (m, 2H), 7.32-7.24 (m, 3H), 6.96-6.93 (m, 2H), 6.87-6.84 (m, 1H), 6.71-6.68 (m, 1H), 4.18 (s, 2H), 4.14 (t, 2H), 4.05 (t, 2H), 2.94-2.87 (m, 4H), 2.63-2.58 (m, 8H), 2.53 (t, 2H), 1.84-1.77 (m, 8H), 1.59-1.51 (m, 2H), 0.89-0.86 (m, 3H); FDMS 569 (M+1); Anal. Calcd for $C_{36}H_{44}N_2O_2S \cdot 1.75C_2H_2O_4$: C, 65.7; H, 6.74; N, 3.78. Found: C, 65.99; N, 6.54; N 3.71.

Example 109

Preparation of 1-[2-[2-Ethyl-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

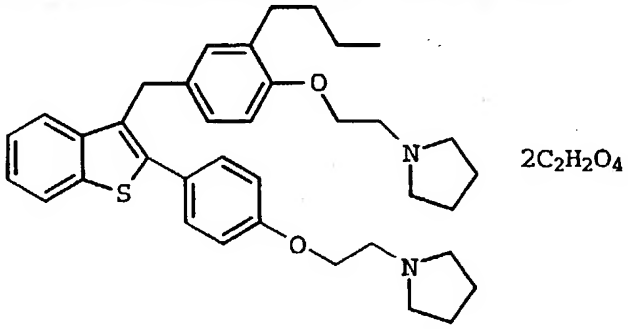


The title compound was prepared in 56% yield from 3-ethyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 101.

^1H NMR (Free base-$CDCl_3$) δ 7.84-7.81 (m, 1H), 7.55-7.51 (m, 1H), 7.45-7.41 (m, 2H), 7.30-7.28 (m, 3H), 6.97-6.93 (m, 2H), 6.87-6.83 (m, 1H), 6.73-6.68 (m, 1H), 4.19 (s, 2H), 4.14 (t, 2H), 4.06 (t, 2H), 2.94-2.87 (m, 4H), 2.65-2.55 (m, 10H), 1.84-1.79 (m, 8H), 1.14 (s, 3H); Exact Mass Calcd for $C_{35}H_{42}N_2O_2S$: 555.3045. Found: 555.3057.

Example 110

Preparation of 1-[2-[2-Butyl-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

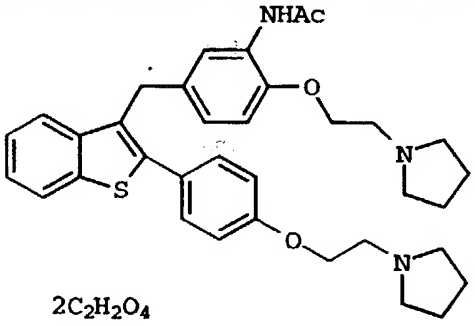


The title compound was prepared in 64% yield from 3-butyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxyphenyl]benzo[*b*]thiophen-3-yl ketone by essentially following the procedure detailed for the preparation of Example 101.

^{1}H NMR (DMSO-d_6) δ 7.98-7.94 (m, 1H), 7.58-7.5 (m, 1H), 7.47 (d, 2H), 7.34-7.32 (m, 2H), 7.1 (d, 2H), 6.9 (s, 1H), 6.8 (s, 2H) 4.5 (bs, 4H), 4.35 (t, 2H), 4.21 (t, 2H), 4.17 (s, 2H), 3.54-3.50 (m, 4H), 3.4-3.2 (m, 8H), 2.5-2.45 (m, 2H), 1.93-1.85 (m, 8H), 1.44-1.39 (m, 2H), 1.26-1.21 (m, 2H), 1.17 (t, 3H); FDMS 582 (M+1); Anal. Calcd for $C_{37}H_{46}N_2O_2S \cdot 1.75C_2H_2O_4$: C, 65.7; H, 6.74; N, 3.78. Found: C, 65.99; N, 6.54; N 3.71.

Example 111

Preparation of 1-[2-[2-Acetamido-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3- yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

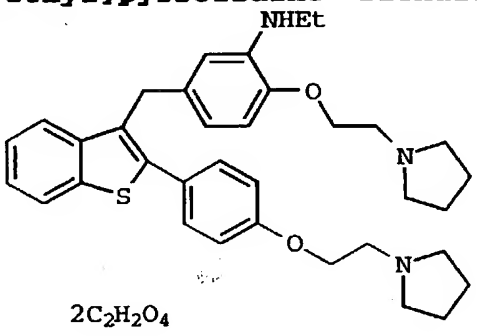


1-[2-[2-Amino-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]ethyl]pyrrolidine (178 mg, 0.33 mmol) was treated with 2 mL of acetic anhydride and 2 mL of pyridine. This was stirred at ambient temperature for 16 h and concentrated under reduced pressure. The resulting oil was mixed with toluene and reconcentrated to dryness. Purification by chromatography (SiO_2; 95/5% THF/Et_3N) afforded 70 mg (0.12 mmol 36%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

^1H NMR (Free base-$CDCl_3$) δ 8.93 (s, 1H), 8.33 (d, 1H), 7.82-7.79 (m, 1H), 7.54-7.50 (m, 1H), 7.46-7.43 (m, 2H), 7.28-7.24 (m, 2H), 6.96-6.93 (m, 2H), 6.73 (d, 1H), 6.62 (d, 1H), 4.22 (s, 2H), 4.13 (t, 2H), 4.08 (t, 2H), 2.91 (t, 2H), 2.77 (t, 2H), 2.63-2.61 (m, 8H), 2.17 (s, 3H), 1.84-1.79 (m, 8H); FDMS 584 (M+1); Anal. Calcd for $C_{35}H_{41}N_3O_3S \cdot 2C_2H_2O_4$: C, 61.32; H, 5.94; N, 5.50. Found: C, 61.59; H, 5.98; N, 5.59.

Example 112

Preparation of 1-[2-[2-Ethylamino-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

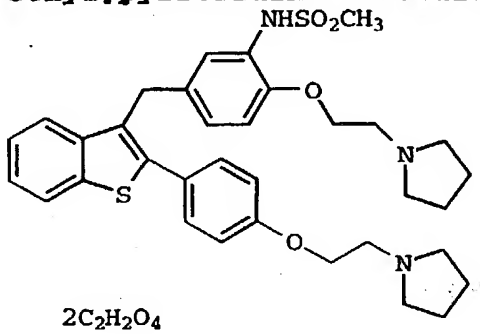


1-[2-[2-Acetamido-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]ethyl]pyrrolidine (600 mg, 1.1 mmol) was dissolved in 20 mL of dry THF and added to a mixture of 20 mL of THF and 84 mg (2.2 mmol) of LAH. The reaction was heated at reflux for 3 h then quenched with 5 mL of EtOAc. To this was added 25 mL of saturated aqueous potassium sodium tartrate. The mixture was stirred for 30 min and extracted with EtOAc (3 X 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to 450 mg of an oil which was purified by chromatrography (SiO_2; 5% MeOH/1% NH_4OH in $CHCl_3$) to afford 55 mg (0.1 mmol; 9%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

^{1}H NMR (Free base-$CDCl_3$) δ 7.82-7.80 (m, 1H), 7.59-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.29-7.27 (m, 2H), 6.96-6.93 (m, 2H), 6.62 (d, 1H), 6.44 (d, 1H), 6.34 (dd,1H), 4.22 (bs, 1H), 4.17 (s, 2H), 4.13 (t, 2H), 4.07 (t, 2H), 3.05 (q, 2H), 2.94-2.86 (m, 4H), 2.65-2.59 (m, 8H), 1.84-1.77 (m, 8H), 1.21 (t, 3H); FDMS 572 (M+3); Anal. Calcd for $C_{35}H_{43}N_3O_2S \cdot 2C_2H_2O_4$: C, 62.47; H, 6.32; N, 5.60. Found: C, 62.46; H, 6.19; N, 5.43.

Example 113

Preparation of 1-[2-[2-Methanesulfonamido-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



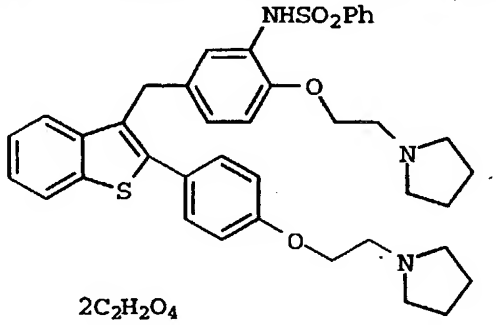
A solution of 1-[2-[2-amino-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]-phenoxy]ethyl]pyrrolidine (750 mg, 1.4 mmol) in 25 mL of CH_2Cl_2 at 0 °C was treated with 159 mg (107 mL, 1.4 mmol) of methanesulfonyl chloride. The reaction was stirred at 0 °C for 8 h then concentrated under vaccuum. The residue was purified by chromatrography (SiO_2; 5% MeOH/1% NH_4OH in $CHCl_3$) to afford 447 mg (0.72 mmol; 52%) of the title compound as an oil which was converted to the dioxalate salt according to the method of Example 1, Part C.

^{1}H NMR (Free base-$CDCl_3$) δ 7.84-7.81 (m, 1H), 7.55-7.53 (m, 1H), 7.52-7.41 (m, 3H), 7.30-7.27 (m, 3H), 6.98-6.94 (m, 2H), 6.85 (d, 1H), 6.76 (dd,1H), 4.21 (s, 2H), 4.15 (s, 2H), 4.09 (t, 2H), 2.93 (t, 2H), 2.82 (s, 3H), 2.65-2.60 (m, 10H), 1.89-1.84 (m, 4H), 1.83-1.80 (m, 4H); FDMS 619 (M+); Anal.

Calcd for $C_{34}H_{41}N_3O_4S_2 \cdot 2C_2H_2O_4 \cdot 1H_2O \cdot 0.1EtOAc$: C, 55.79; H, 5.83; N, 5.08. Found: C, 56.01; H, 5.98; N, 4.71.

Example 114

Preparation of 1-[2-[2-Phenylsulfonamido-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

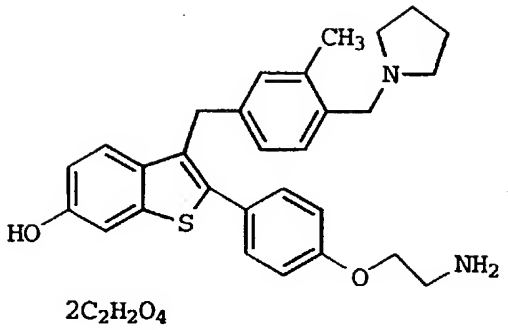


This compound was prepared in 35% yield from phenylsulfonyl chloride and 1-[2-[2-amino-4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]-phenoxy]ethyl]pyrrolidine by essentially following the procedure detailed for the preparation of Example 113.

^1H NMR (Free base-$CDCl_3$) δ 8.1 (bs, 1H), 7.84-7.81 (m, 1H), 7.58-7.54 (m, 2H), 7.49-7.35 (m, 5H), 7.31-7.21 (m, 4H), 6.98-6.95 (m, 2H), 6.72-6.78 (m, 2H), 4.17-4.12 (m, 4H), 3.92 (t, 2H), 2.92 (t, 2H), 265-2.54 (m, 10H), 1.94-193 (m, 4H), 1.83-1.79 (m, 4H); FDMS 682 (M+1); Anal. Calcd for $C_{39}H_{43}N_3O_4S_2 \cdot 1.5C_2H_2O_4 \cdot 0.2H_2O$: C, 61.48; H, 5.70; N, 5.12. Found: C, 61.25; H, 6.05; N, 4.97.

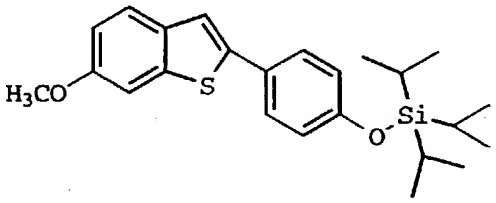
Example 115

Preparation of 2-[4-(2-Aminoethoxy)phenyl]-6-hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]-benzo[*b*]thiophene Dioxalate.



$2C_2H_2O_4$

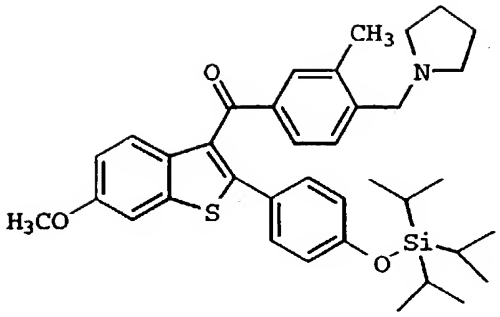
Part A. 4-(6-Methoxybenzo[*b*]thiophen-2-yl)phenyl Triisopropylsilyl Ether.



A solution of 6-methoxy-2-(4-hydroxyphenyl)benzo[*b*]-thiophene (16 g, 62.4 mmol) in 160 mL of dry DMF was treated with Et_3N (12.6 g, 124.8 mmol) at 0 °C. To this was added in a dropwise manner 28.7 g (93.6 mmol) of triisopropyl trifluoromethanesulfonate. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h before being poured into 200 mL of saturated aqueous $NaHCO_3$ and 300 mL of brine. This was extracted with 10% EtOAc in hexanes (3 X 200 mL). The combined extracts were washed with brine (2 X 300 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give 32 g of an oil which was purified by chromatrography (SiO_2; 5% EtOAc in Hexanes) to yield 12.3 g (29.8 mmol, 48%) of the silyl ether as a white solid.

FDMS 412 (M+); Anal. Calcd for $C_{24}H_{32}O_2SSi \cdot 0.65EtOAc$: C, 68.50; H, 8.18. Found: C, 68.55; H, 8.16.

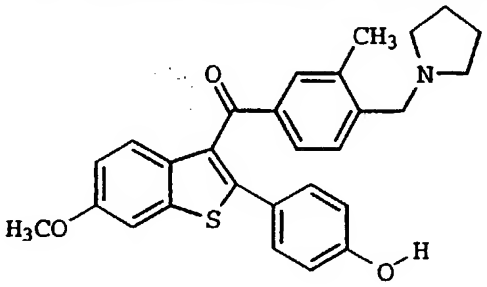
Part B. 6-Methoxy-2-[4-[(triisopropylsilyl)oxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone



The ketone was prepared in 83% yield from the above benzothiophene, $TiCl_4$, and 3-methyl-4-[(1-pyrrolidinyl)methyl]benzoic acid hydrochloride by essentially following the procedure detailed for the preparation of Example 96, Part C.

FDMS 613 (M+); Anal. Calcd for $C_{37}H_{47}NO_3SSi \cdot 0.23CHCl_3$: C, 69.5; H, 7.40; N, 2.18. Found: C, 69.43; H, 7.48; N, 2.34.

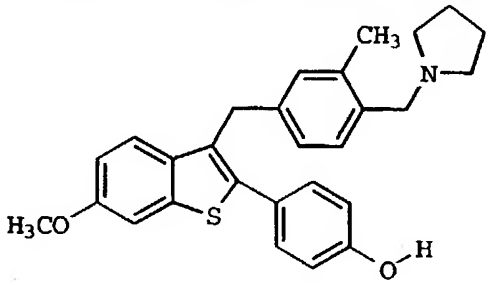
Part C. 2-(4-Hydoxyphenyl)-6-methoxybenzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



A solution of the above silyl ether (5.23 g, 8.5 mmol) in THF (50 mL) was treated with a 1 M THF solution of tetrabutylammonium fluoride (8.5 mL) at ambient temperature. The reaction was stirred for 16 h, concentrated *in vacuo*, mixed with $CHCl_3$ and purified by chromatography (SiO_2; 2.5% MeOH in $CHCl_3$) to afford 3.8 g (8.3 mmol, 98%) of the phenoxy product as an oil.

^{1}H NMR (Free base-$CDCl_3$) δ 7.65 (d, 1H), 7.53 (s, 1H), 7.48 (d, 1H), 7.32 (d, 1H), 7.21-7.16 (m, 3H), 6.99-6.97 (m, 1H), 6.57 (d, 2H), 5.75 (bs, 1H), 3.89 (s, 3H), 3.59 (s, 2H), 2.6-2.5 (m, 4H), 2.25 (s, 3H), 1.85-1.78 (m, 4H).

Part D. 2-(4-Hydroxyphenyl)-6-methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]benzo[*b*]thiophene.



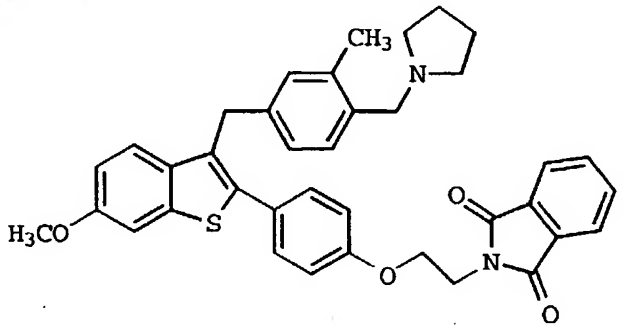
A solution of the above ketone (4 g, 8.7 mmol) in THF (100 mL) was cooled to 0 °C under N_2 and treated with a 1 M solution of LAH in THF (17.4 mL). The bath was removed and the reaction was stirred at ambient temperature for 2 h. It was quenched by the dropwise addition of 500 mL of H_2O at 0 °C, followed by 200 mL of EtOAc and 50 g diatomaceous earth. The mixture was filtered, the layers were separated, and the organic layer was dried over $MgSO_4$ and concentrated to give 4 g of the benzyl alcohol.

The foam was dissolved in 100 mL of $ClCH_2CH_2Cl$ and cooled to 0 °C under N_2. The colorless solution was treated with 5.1 g (43.5 mmol) of Et_3SiH and 10 g (87.4 mmol) of TFA. The reaction was stirred at 0 °C for 1 h then quenched with 50 mL of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated to an oil. Purification by chromatography (SiO_2; 65/30/5% Hex/THF/Et_3N) afforded 3.5 g (7.9 mmol 91%) of the methylene compound as a foam.

^{1}H NMR (Free base-DMSO-d_6) δ 7.55 (d, 1H), 7.4 (d, 1H), 7.36 (d, 2H), 7.1 (d, 1H), 6.95-6.80 (m, 5H), 4.15 (s, 2H), 3.80

(s, 3H), 3.4 (s, 2H), 3.3 (bs, 1H), 2.43-2.30 (m, 4H), 2.20 (s, 3H), 1.65-1.60 (m, 4H); FDMS 443 (M+).

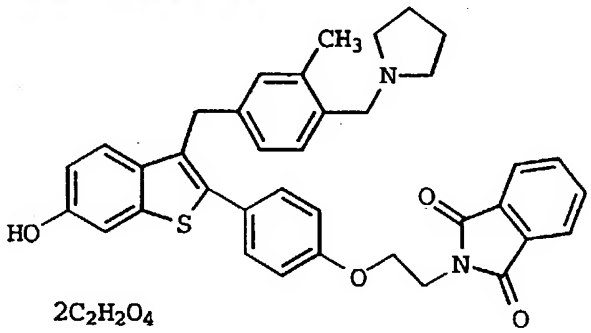
Part E. 6-Methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(phthalimido)ethoxy]phenyl]-benzo[*b*]thiophene.



The named compound was prepared in 29% yield from 2-(4-hydroxyphenyl)-6-methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)-methyl]benzyl]benzo[*b*]thiophene and hydroxyethylphthalimide by essentially following the procedure detailed for the preparation of Example 20, Part B.

FDMS 616 (M+); Anal. Calcd for $C_{38}H_{36}N_2O_4S \cdot 1.2H_2O$: C, 71.49; H, 6.06; N, 4.39. Found: C, 71.58; H, 6.10; N, 4.36.

Part F. 6-Hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(phthalimidyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.



$2C_2H_2O_4$

This compound was prepared in 52% yield from the above 6-methoxybenzo[*b*]thiophene by essentially following the procedure detailed for the preparation of Example 1, Part D.

^{1}H NMR (Free base-$CDCl_3$) δ 7.88-7.84 (m, 2H), 7.74-7.71 (m, 2H), 7.34-7.29 (m, 2H), 7.19-7.15 (m, 2H), 7.1 (d, 1H), 6.92 (s, 1H), 6.88-6.84 (m, 3H), 6.41-6.37 (m, 1H), 4.24 (t, 2H), 4.14-4.10 (m, 3H), 3.61 (s, 2H), 2.69-2.61 (m, 6H), 2.27 (s, 3H), 1.80-1.79 (m, 4H); FDMS 603 (M+1).

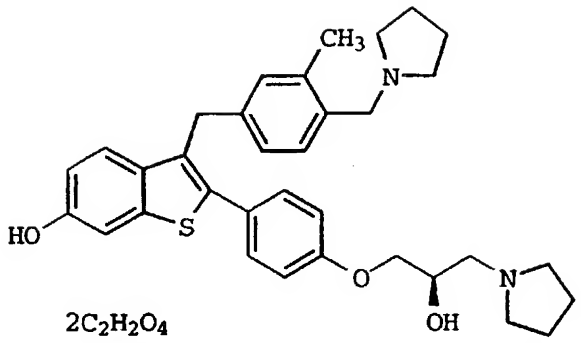
Part G. 2-[4-(2-Aminoethoxy)phenyl]-6-hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]-benzo[*b*]thiophene Dioxalate.

A mixture of the above phthalimide (0.4 g, 0.66 mmol) and 1 mL hydrazine hydrate in 50 mL of EtOH was heated at reflux for 1 h then concentrated to dryness under reduced pressure. The residue was mixed with 50 mL of 1 N aqueous NaOH and 50 mL of 10% MeOH in EtOAc. The layers were separated and the aqueous layer was extracted with 25 mL of 10% MeOH in EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated to dryness and purified by chromatrography (SiO_2; 5% MeOH, 1% NH_4OH in $CHCl_3$) to afford 230 mg (0.49 mmol, 74%) of the title product as a solid which was converted to its dioxalate salt according to the method of Example 1, Part C.

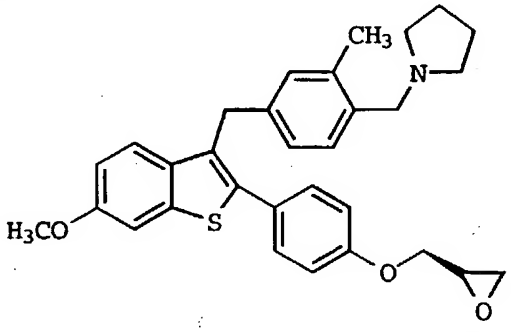
^{1}H NMR (Free base-$CDCl_3$) δ 8.3 (s, 1H), 7.39 (d, 1H), 7.37-7.2 (m, 3H), 7.05 (d, 1H), 7.0 (d, 2H), 6.85 (s, 1H), 6.82-6.7 (m, 2H), 4.08 (s, 2H), 3.94 (t, 2H), 3.41 (s, 2H), 3.34 (bs, 2H), 2.88 (t, 2H), 2.39-2.35 (m, 4H), 2.18 (s, 3H), 1.65-1.6 (m, 4H); FDMS 472 (M+).

Example 116

Preparation of (R)-6-Hydroxy-2-[4-[2-hydroxy-3-(1-pyrrolidinyl)propoxy]phenyl]-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]benzo[*b*]thiophene Dioxalate.



Part A. (2R)-2-[4-(Glycidyloxy)phenyl]-6-methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]-benzo[*b*]thiophene.

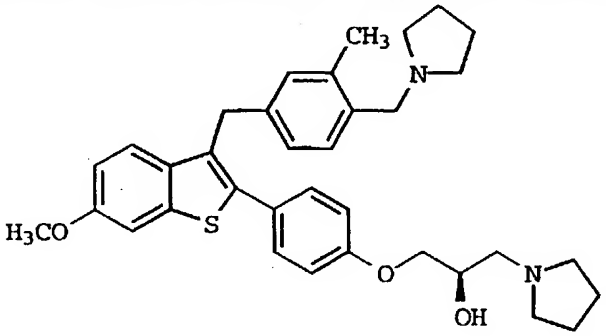


A 60% dispersion of sodium hydride (141 mg,3.5 mmol) was rinsed with hexanes under a nitrogen atmosphere and dried under reduced pressure. To this was added a solution of the hydroxyphenylbenzo[*b*]thiophene of Example 115, Part C (1.3 g, 2.9 mmol) in 30 mL of dry DMF and stirred for 1 h at ambient temperature. The mixture was treated with (2R)-(-)-glycidyl-3-nitrobenzenesulfonate, then stirred for 16 h at ambient temperature. The reaction was poured into a mixture of 50 mL of saturated aqueous $NaHCO_3$, 100 mL of saturated aqueous NaCl and 100 mL of H_2O. It was extracted with EtOAc (3 X 100 mL). The extracts were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by chromatrography to give 1.2 g (2.4 mmol, 81%) of the product as an oil.

^1H NMR (Free base-$CDCl_3$) δ 7.45-7.38 (m, 5H), 7.33 (d, 1H), 7.18 (d, 1H), 6.97-6.88 (m, 3H), 4.23-4.18 (m, 1H), 4.18 (s, 2H), 4.02-3.96 (m, 1H), 3.88 (m, 3H), 3.55 (s, 2H), 3.39-3.37

(m, 1H), 2.95-2.92 (m, 1H), 2.79-2.71 (m, 1H), 2.55-2.49 (m, 4H), 2.3 (s, 3H), 1.8-1.76 (m, 4H).

Part B. (R)-2-[4-[2-Hydroxy-3-(1-pyrrolidinyl)-propoxy]phenyl]-6-methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]benzo[*b*]thiophene.



The above (2R)-[(glycidyloxy)phenyl]benzo[*b*]thiophene (1.18 g, 2.4 mmol) was mixed with pyrrolidine (338 mg, 4.8 mmol) and MeOH (50 mL). The mixture was heated at reflux for 6 h, concentrated to an oil and purified by chromatrography (SiO_2; 30% THF/5% Et_3N in hexanes) to afford 1 g of the named product as an oil.

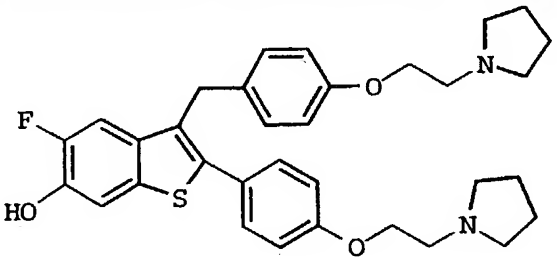
Part C. (R)-6-Hydroxy-2-[4-[2-hydroxy-3-(1-pyrrolidinyl)propoxy]phenyl]-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 61% yield from the above methoxybenzo[*b*]thiophene by essentially following the procedure detailed for the preparation of Example 115, Parts F and G.

^1H NMR (DMSO-d_6) δ 7.4-6.7 (m, 11H), 4.3-3.9 (m, 9H), 3.4-3.2 (m, 7H), 3.2-2.29 (m, 4H), 2.25 (s, 3H), 2.00-1.7 (m, 10H); FDMS 557 (M+1).

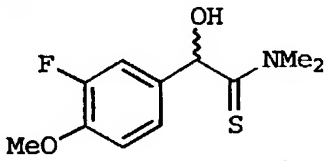
Example 117

Preparation of 1-[2-[4-[[5-Fluoro-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

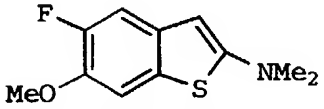
Part A. N,N-Dimethyl-3-fluoro-4-methoxy-α-hydroxy-phenylthioacetamide.



A -78 °C solution of 18.7 mL (142.7 mmol) of diisopropylamine in 100 mL of THF was treated with 89.0 mL (1.6 M in hexanes; 142.2 mmol) of *n*-BuLi. The reaction mixture was stirred at -78 °C for 15 min and at 0 °C for 0.5 h. After cooling back to -78 °C, a solution of 20.0 g (129.7 mmol) of 3-fluoro-4-anisaldehyde and 12.2 mL (143.6 mmol) of N,N-dimethylthioformamide in 100 mL of THF was added slowly. After complete addition, the reaction was stirred at -78 °C for 15 min and was quenched with a solution of 15 mL of HOAc in 100 mL of MeOH. The mixture was concentrated *in vacuo* and the residue was partitioned between 250 mL of saturated aqueous $NaHCO_3$ and 250 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 22.4 g of an oily solid. Trituration with Et_2O afforded 16.21 g (66.6 mmol; 51%) of the title compound as a light yellow solid.

Anal. Calcd for $C_{11}H_{14}FNO_2S$: C, 54.30; H, 5.80; N, 5.76. Found: C, 54.00; H, 5.86; N, 5.77.

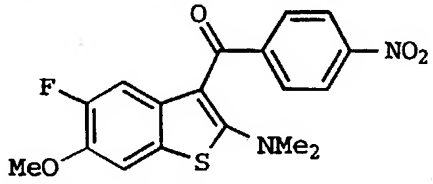
Part B. 2-Dimethylamino-5-fluoro-6-methoxy-benzo[*b*]thiophene.



A solution of 16.6 g (68.2 mmol) of N,N-dimethyl-3-fluoro-4-methoxy-2-hydroxyphenylthioacetamide (Part A) in 400 mL of CH_2Cl_2 was treated with 22.0 mL (339.0 mmol) of $MeSO_3H$ in a dropwise manner. The reaction was stirred at room temperature for 4 h, was cooled to 0 °C, and was quenched by the careful addition of 500 mL of saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with EtOAc (5x200 mL). The combined organic layers were washed with 500 mL of saturated aqueous $NaHCO_3$ and 500 mL of H_2O, dried over Na_2SO_4, and filitered. Evaporation of the solvent *in vacuo* afforded 21.4 g of an oil which was purified by flash chormatography (SiO_2; gradient of 10% then 20% EtOAc in hexanes) to give 2.87 g (12.7 mmol; 19%) of the title compound as a light pink solid.

FDMS 225 (M+); Anal. Calcd for $C_{11}H_{12}FNOS$: C, 58.65; H, 5.37; N, 6.22. Found: C, 58.37; H, 5.42; N, 6.17.

Part C. 2-Dimethylamino-5-fluoro-6-methoxy-benzo[*b*]thiophene-3-yl 4-Nitrophenyl Ketone.

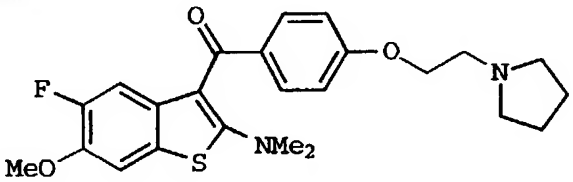


A solution of 1.08 g (4.82 mmol) of 2-dimethylamino-5-fluoro-6-methoxybenzo[*b*]thiophene (Part B) in 15 mL of chlorobenzene was treated with 0.99 g (5.31 mmol) of 4-nitrobenzoyl chloride. The reaction was stirred at room temperature for 17 h and was diluted with 100 mL of EtOAc. The solution was washed sequentially with 2 N aqueous NaOH (2 x 50 mL), H_2O (50 mL) and brine (50 mL), then dried over

Na_2SO_4, and filtered. Evaporation of the solvent *in vacuo* afforded 2.1 g of a dark solid which was purified by flash chromatography (SiO_2; gradient of 10% then 20% then 40% EtOAc in hexanes) to give 0.27 g of starting material and 1.25 g (3.34 mmol; 93% based on consumed starting material) of the title compound.

FDMS 374 (M+); Anal. Calcd for $C_{18}H_{15}FN_2O_4S$: C, 57.75; H, 4.04; N, 7.48. Found: C, 58.04; H, 3.98; N, 7.50.

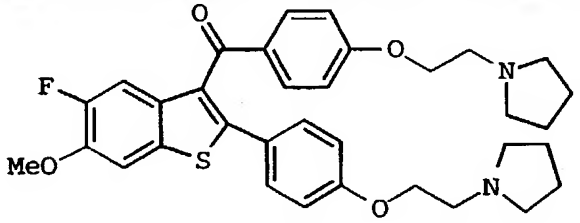
Part D. 2-Dimethylamino-5-fluoro-6-methoxybenzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl Ketone.



A mixture of 2.0 g (5.34 mmol) of 2-dimethylamino-5-fluoro-6-methoxybenzo[*b*]thiophene-3-yl 4-nitrophenyl ketone (Part C) and 1.4 g (60% dispersion in mineral oil; 35.0 mmol; washed with hexanes) of NaH in 60 mL of DMF was treated with a solution of 3.75 mL (32.1 mmol) of 1-(2-hydroxyethyl)-pyrrolidine in 10 mL of DMF in such rate to control the effervescence. After complete addition, the reaction was stirred at room temperature for 1 h and was quenched by the careful addition of 5 mL of MeOH. The mixture was diluted with 200 mL of EtOAc and was poured into 200 mL of H_2O. The two layers were separated and the organic phase was washed with H_2O (2 x 100 mL) and brine (100 mL). The organic phase was dried over K_2CO_3, filtered, and concentrated *in vacuo* to give 5.21 g of an amber oil. Purification by flash chromatography (SiO_2; gradient of 2% then 5% MeOH in CH_2Cl_2) afforded 2.10 g (4.74 mmol; 89%) of the title compound as a bright yellow oil.

FDMS 442 (M+); Anal. Calcd for $C_{24}H_{27}FN_2O_3S$: C, 65.14; H, 6.15; N, 6.33. Found: C, 65.08; H, 6.43; N, 6.29.

Part E. 5-Fluoro-6-methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone Dioxalate.

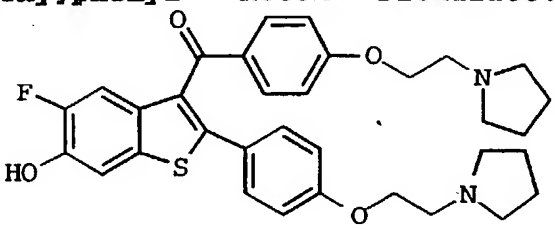


2 $C_2H_2O_4$

Magnesium turnings (69 gm; 2.84 mmol) were placed in a 3-neck round bottom equipped with a stir bar, nitrogen inlet, dropping funnel and reflux condensor and flame-dried under a stream of nitrogen. THF (5 mL) was added to the reaction vessel followed by a solution of 732 mg (2.71 mg) of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine and a small I_2 crystal. The vessel contents were heated to mild reflux for 7 h at which time all the Mg had been consumed. The reaction was cooled to 0 °C and was added via a cannula to a 0 °C solution of 1.00 g (2.26 mmol) of 2-dimethylamino-5-fluoro-6-methoxy-benzo[*b*]thiophene-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part D) in 10 mL of THF. The mixture was stirred at 0 °C for 16 h, was quenched with 10 mL of H_2O, and was acidified to pH 7-8 with 1 N aqueous HCl. The mixture was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts were washed with H_2O, dried over K_2CO_3, filtered, and concentrated *in vacuo* to give 1.53 g of an oil. Purification by flash chromatography (SiO_2; 4:11:84 TEA/THF/hexanes) afforded 1.18 g (2.12 mmol; 78%) of the title compound as an oil. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 589 (M+1); Anal. Calcd for $C_{34}H_{37}FN_2O_4S \cdot 2\ C_2H_2O_4$: C, 57.22; H, 5.18; N, 3.51. Found: C, 57.48; H, 5.42; N, 3.54.

Part F. 5-Fluoro-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

By essentially following the procedures outlined in Example 1, Part D, the title compound was prepared in 61% yield starting from 5-fluoro-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part E). A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 575 (M+1); Anal. Calcd for $C_{33}H_{35}FN_2O_4S \cdot 2\ C_2H_2O_4$: C, 61.49; H, 5.44; N, 3.88. Found: C, 61.30; H, 5.67; N, 4.09.

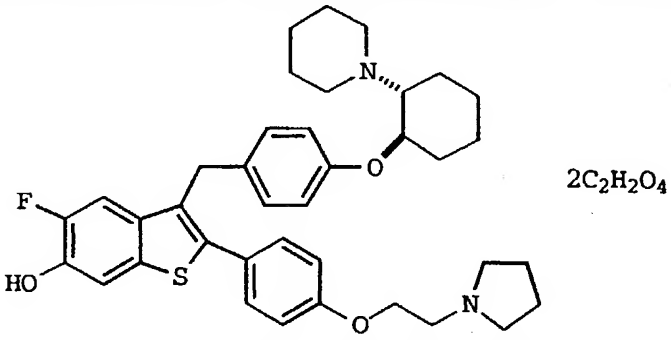
Part G. 1-[2-[4-[[5-Fluoro-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.

The title compound was prepared in 64% yield from 5-fluoro-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part F) by essentially following the procedure detailed in Example 3, Part E. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

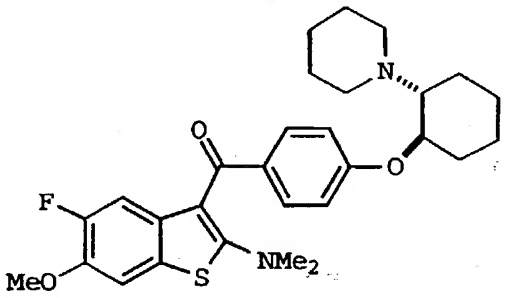
FDMS 561 (M+1); Anal. Calcd for $C_{33}H_{37}FN_2O_3S \cdot 2\ C_2H_2O_4$: C, 59.99; H, 5.58; N, 3.78. Found: C, 59.76; H, 5.67; N, 3.68.

Example 118

Preparation of (±)-5-Fluoro-6-hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



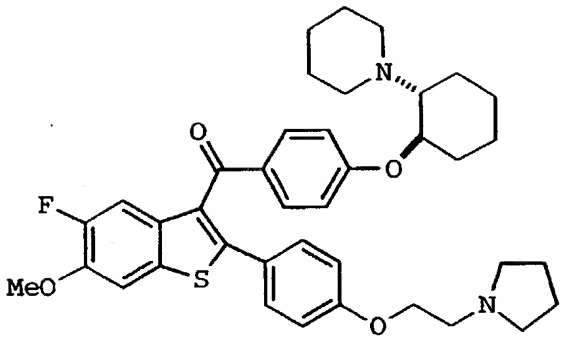
Part A. 2-Dimethylamino-5-fluoro-6-methoxybenzo[*b*]thiophene-3-yl 4-[[*trans*-2-(1-Piperidyl)-cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 51% from 2-dimethylamino-5-fluoro-6-methoxybenzo[*b*]thiophene-3-yl 4-nitrophenyl ketone (Example 117, Part C) and (±)-*trans*-2-(1-piperidyl)cyclohexanol by essentially following the procedure detailed in Example 117, Part D.

FDMS 510 (M+); Anal. Calcd for $C_{29}H_{35}FN_2O_3S$: C, 68.21; H, 6.91; N, 5.49. Found: C, 68.32; H, 7.18; N, 5.39.

Part B. (±)-5-Fluoro-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

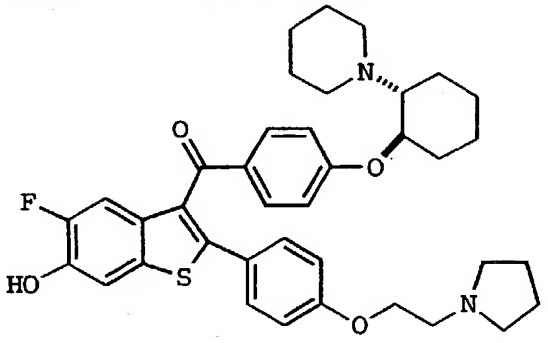


2 $C_2H_2O_4$

The title compound was prepared in 72% yield (based on consumed starting material) from 2-dimethylamino-5-fluoro-6-methoxybenzo[*b*]thiophene-3-yl 4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]phenyl ketone (Part A) by essentially following the procedure detailed in Example 117, Part E. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 657 (M+1); Anal. Calcd for $C_{39}H_{45}FN_2O_4S \cdot 2\ C_2H_2O_4$: C, 61.71; H, 5.90; N, 3.35. Found: C, 61.45; H, 6.07; N, 3.63.

Part C. (±)-5-Fluoro-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

The title compound was prepared in 70% yield from (±)-5-fluoro-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-piperidyl)cyclohexyl]-oxy]phenyl ketone (Part B) by essentially following the procedure detailed in Example 1, Part D. A sample was

converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 643 (M+1); Anal. Calcd for $C_{38}H_{43}FN_2O_4S \cdot 2\ C_2H_2O_4$: C, 61.30; H, 5.76; N, 3.40. Found: C, 61.04; H, 5.84; N, 3.45.

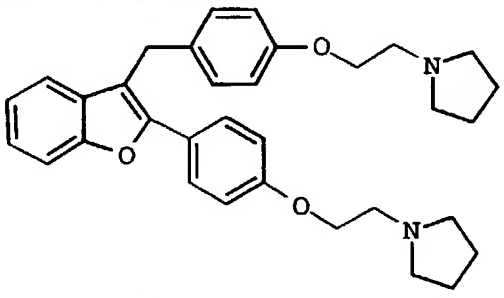
Part D. (±)-5-Fluoro-6-hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 70% yield from (±)-5-fluoro-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]phenyl ketone (Part C) by essentially following the procedure detailed in Example 3, Part E. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 629 (M+1); Anal. Calcd for $C_{38}H_{45}FN_2O_3S \cdot 2\ C_2H_2O_4$: C, 62.36; H, 6.11; N, 3.46. Found: C, 62.60; H, 6.11; N, 3.50.

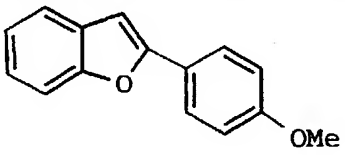
Example 119

Preparation of 1-[2-[4-[[2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzofuran-3-yl]methyl]phenoxy]ethyl]-pyrrolidine Dioxalate.



2 $C_2H_2O_4$

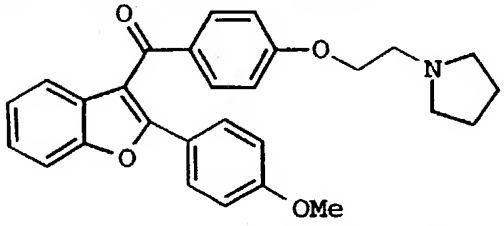
Part A. 2-(4-Methoxyphenyl)benzofuran.



A solution of 46.0 g (0.39 mole) of benzofuran in 100 mL of Et_2O was treated with 0.40 mol (1.6 M in hexanes) of *n*-BuLi at such a rate as to keep the reaction temperature below 25 °C. The mixture was stirred for 15 min and was added to a 10 °C solution of 57.2 g (0.40 mole) of CuBr in 100 mL of Et_2O at a rate so as to keep the reaction temperature below 10 °C. The mixture was allowed to reach room temperature over 0.5 h and was treated with a solution of 93.6 g of iodoanisole in 300 mL of pyridine. The mixture was heated to 110 °C for 3 h, allowing the Et_2O to boil off. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 3 L of EtOAc. The organic layer was washed several times with 2 N aqueous HCl and once with H_2O, dried over $MgSO_4$, and filtered. Concentration *in vacuo* afforded a residue which was recrystallized from MeOH to afford 44.5 g of the title compound as a solid.

mp 145-147 °C.

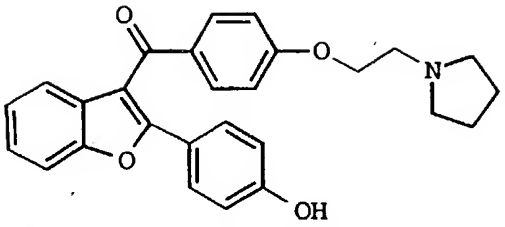
Part B. 2-(4-Methoxyphenyl)benzofuran-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone.



The title compound was prepared in 79% yield from 2-(4-methoxyphenyl)benzofuran (Part A) and 4-[2-(1-pyrrolidinyl)-ethoxy]benzoic acid hydrochloride by essentially following the procedure detailed in Example 1, Part C.

mp 92-95 °C; FDMS 441 (M+);

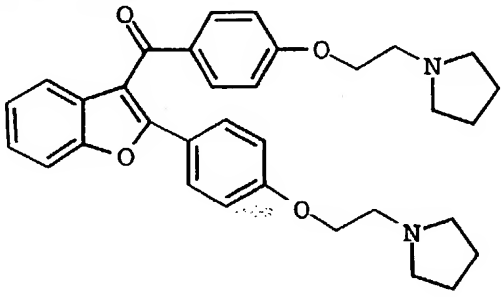
Part C. 2-(4-Hydroxyphenyl)benzofuran-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone.



By essentially following the procedures described in Example 1, Part D, the title compound was prepared in 81% yield from 2-(4-methoxyphenyl)benzofuran-2-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part B).

FDMS 427 (M+); Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.38. Found: C, 75.59; H, 5.96; N, 3.47.

Part D. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzofuran-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

By essentially following the procedure described in Example 3, Part D, the title compound was prepared in 76% yield from 2-(4-hydroxyphenyl)benzofuran-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part D) and 1-(2-chloroethyl)pyrrolidine hydrochloride. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 525 (M+1). Anal. Calcd for $C_{33}H_{36}N_2O_4 \cdot 2\ C_2H_2O_4$ C, 63.06; H, 5.72 N, 3.98. Found: C, 62.66 H, 5.75; N, 4.06.

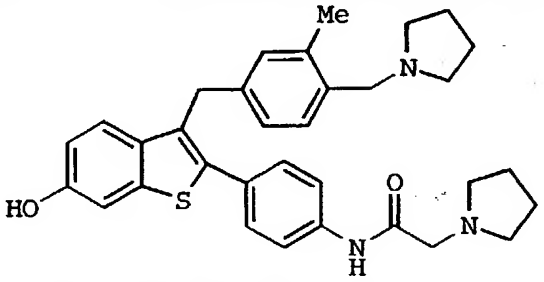
Part E. 1-[2-[4-[[2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzofuran-3-yl]methyl]phenoxy]ethyl]-pyrrolidine Dioxalate.

By essentially following the procedure detailed in Example 3, Part E, the title compound was prepared in 82% yield from 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzofuran-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part D). A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 511 (M+1); Anal. Calcd for $C_{33}H_{38}N_2O_3 \cdot 2\ C_2H_2O_4 \cdot H_2O$ C, 62.70; H, 6.26 N, 3.95. Found: C, 62.83 H, 6.13; N, 3.98.

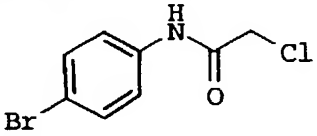
Example 120

Preparation of *N*-[4-[6-Hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiphen-2-yl]phenyl]-α-(1-pyrrolidinyl)acetamide Dioxalate.



1.7 $C_2H_2O_4$

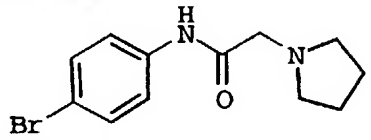
Part A. N-(4-Bromophenyl)-α-chloroacetamide.



A mixture of 8.60 g (0.05 mol) of 4-bromoaniline, 10.60 g (0.10 mol) of Na_2CO_3, and 6.78 g (0.06 mol) of chloroacetyl chloride in 100 mL of acetone was stirred at ambient temperature for 3 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give 11.4 g of analytically pure title compound as light crystals.

FDMS 248 (M+); Anal. Calcd for $C_8H_7BrClNO$: C, 38.67; H, 2.84; N, 5.64. Found: C, 38.45; H, 2.83; N, 5.56.

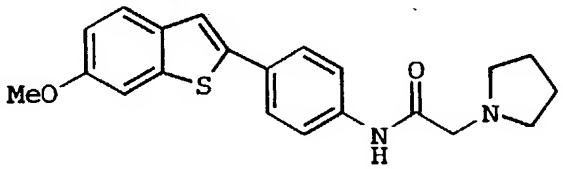
Part B. N-(4-Bromophenyl)-α-(1-Pyrrolidinyl)acetamide.



A solution of 5.0 g (0.02 mol) of N-(4-bromophenyl)-α-chloroacetamide (Part A) and 5.05 mL (0.06 mol) of pyrrolidine in 100 mL of THF was stirred overnight at ambient temperature. The mixture was concentrated *in vacuo* and the residue was partitioned between H_2O and EtOAc. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to afford 5.74 g of analytically pure title compound as crystals.

mp 60-63 °C; Anal. Calcd for $C_{12}H_{15}BrN_2O$: C, 50.90; H, 5.34; N, 9.89. Found: C, 50.62; H, 5.39; N, 9.74.

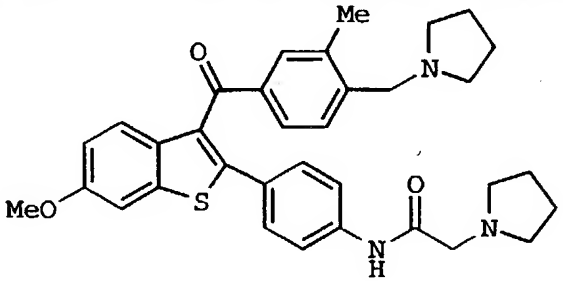
Part C. N-[4-(6-Methoxybenzo[*b*]thiophen-2-yl)phenyl]-α-(1-pyrrolidinyl)acetamide.



By essentially following the procedures described in Example 1, Part B, the title compound was prepared in 97% yield from *N*-(4-bromophenyl)-α-(1-pyrrolidinyl)acetamide (Part B) and 6-methoxybenzo[*b*]thiophene-2-boronic acid (Example 1, Part A).

IR ($CHCl_3$) 1684; FDMS 366 (M+).

Part D. N-[4-[6-Methoxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]carbonyl]benzo[*b*]thiophen-2-yl]phenyl]-α-(1-pyrrolidinyl)acetamide Dioxalate.



$2 \cdot C_2H_2O_4$

By essentially following the procedures described in Example 1, Part C, the title compound was prepared in 68% yield from the product of Part C and 3-methyl-4-[(1-pyrrolidinyl)methyl]benzoic acid. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

IR ($CHCl_3$) 1701, 1640; FDMS 567 (M+). Anal. Calcd for $C_{34}H_{37}N_3O_3S \cdot 2\ C_2H_2O_4$ C, 61.03; H, 5.53 N, 5.62. Found: C, 60.99 H, 5.72; N, 5.38.

Part E. N-[4-[6-Hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]carbonyl]benzo[*b*]thiophen-2-yl]phenyl]-α-(1-pyrrolidinyl)acetamide.

By essentially following the procedures described in Example 1, Part D, the title compound was prepared from the product of Part D. A sample was converted to the oxalate salt according to the method described in Example 1, Part C.

FDMS 554 (M+1). Anal. Calcd for $C_{33}H_{35}N_3O_3S.1.7\ C_2H_2O_4$ C, 61.86; H, 5.48 N, 5.95. Found: C, 62.15 H, 5.47; N, 5.78.

Part F. N-[4-[6-Hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]phenyl]-α-(1-pyrrolidinyl)acetamide Dioxalate.

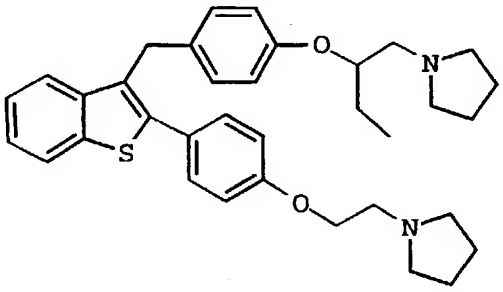
By essentially following the procedures described in Example 3, Part E, the title compound was prepared from the

product of Part E above. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

IR (KBr) 1696, 1607; FDMS 540 (M+1). Anal. Calcd for $C_{33}H_{37}N_3O_2S \cdot 1.7\ C_2H_2O_4$ C, 61.86; H, 5.48 N, 5.95. Found: C, 62.15 H, 5.47; N, 5.78.

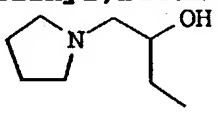
Example 121

Preparation of 1-[2-[4-[3-[[4-[1-Ethyl-2-(1-pyrrolidinyl)ethoxy]phenyl]methyl]benzo[*b*]thiophen-2-yl]-phenoxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

Part A. 1-(1-Pyrrolidinyl)butan-2-ol.

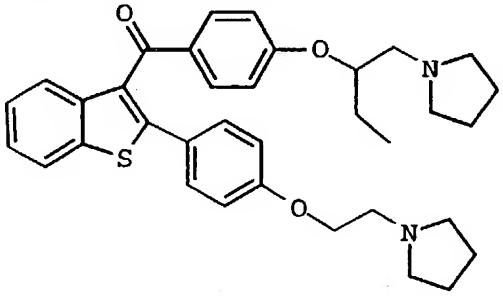


A mixture of 2.6 mL (31.1 mmol) of pyrrolidine and 21.6 g (156.3 mmol) of K_2CO_3 in 100 mL of DMF was treated with 4.7 g (3.20 mL; 90% tech. grade; 28.2 mmol) of 1-bromo-2-butanone and the reaction was stirred at ambient temperature for 2 h. The mixture was filtered and concentrated *in vacuo*. The residue was taken up in 100 mL of 1 N aqueous HCl and the solution was washed with 100 mL of EtOAc. The aqueous layer was basified to pH 13 with solid KOH and was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over K_2CO_3, filtered, and concentrated *in vacuo* to give 1.6 g of an oil. The oil was taken up in 100 mL of THF and the solution was treated with 860 mg (22.7 mmol) of $LiAlH_4$ at room temperature for 3 h, and then quenched by the sequential addition of 60 mL of H_2O, 60 mL of 2 N aqueous NaOH, and 60

mL of H_2O at 0 °C. The mixture was filtered through diatomaceous earth, and the organic solvent was evaporated *in vacuo*. The aqueous layer was extracted with EtOAc (4x100 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated *in vacuo* to give 1.40 g of an oil. Purification by flash chromatography (SiO_2; 3% MeOH in $CHCl_3$ saturated with NH_4OH) afforded 0.95 g of the title compound as an oil.

FDMS 144 (M+1); Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.34; H, 12.07; N, 10.08.

Part B. 4-[1-Ethyl-2-(1-pyrrolidinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



2 $C_2H_2O_4$

A 0 °C mixture of 75.0 mg (1.88 mmol)of NaH and 550 mg (1.23 mmol) of 4-fluorophenyl 2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thien-3-yl ketone in 10 mL of DMF was treated with a solution of 190 mg (1.33 mmol) of the alcohol from Part A above in 5 mL of DMF at 60 °C for 13 h. After cooling to room temperature, the mixture was poured into 100 mL of brine and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL) and brine (100 mL), dried over K_2CO_3, filtered, and concentrated *in vacuo* to give 780 mg of an oil. Purification by radial chromatography (SiO_2; 5% MeOH in $CHCl_3$ saturated with NH_4OH) afforded 210 mg (0.37 mmol; 30%) of the title compound as an oil. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 659 (M+1+$C_2H_2O_4$); Anal. Calcd for $C_{35}H_{40}N_2O_3S.2\ C_2H_2O_4$: C, 62.55; H, 5.92; N, 3.74. Found: C, 62.32; H, 6.15; N, 3.51.

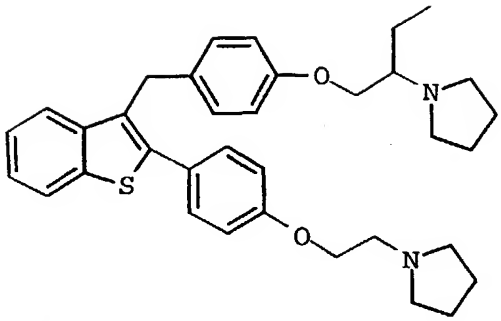
Part C. 1-[2-[4-[3-[[4-[1-Ethyl-2-(1-pyrrolidinyl)-ethoxy]phenyl]methyl]benzo[*b*]thiophen-2-yl]phenoxy]-ethyl]pyrrolidine Dioxalate.

A 0 °C solution of the ketone from Part B (135 mg, 0.237 mmol) in 2.5 mL of anhydrous THF was treated with DIBAL-H (593 µL, 0.593 mmol, 1.0 M solution in toluene) dropwise via a syringe. After 1 h at 0 °C, the excess DIBAL-H was quenched with excess MeOH (approximately 1 mL). A solution of 5 mL of saturated Na^+K^+ tartrate and 5 mL of EtOAc were added, and the biphasic mixture was vigorously stirred for 1.5 h at ambient temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was dissolved in 2.5 mL of 1,2-dichloroethane and Et_3SiH (183 µL, 2.37 mmol). Upon cooling to 0 °C, TFA (265 µL, 1.66 mmol) was added in a dropwise fashion. After 1.5 h, the reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by radial chromatography (SiO_2; gradient 2.5% to 5% MeOH in $CHCl_3$, saturated with NH_4OH) afforded 62 mg (0.112 mmol; 47%) of a yellow oil. The free base was converted to the title dioxalate salt according to the conditions described in Example 1, Part C.

FDMS 555 (M+1); Anal. calcd for $C_{35}H_{42}N_2O_2S\cdot 2C_2H_2O_4$: C, 63.74; H, 6.31; N, 3.81. Found: C, 63.52; H, 6.26; N, 3.73.

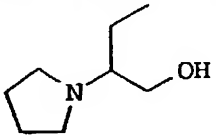
Example 122

Preparation of 1-[2-[4-[3-[[4-[2-(1-Pyrrolidinyl)-butoxy]]phenyl]methyl]benzo[*b*]thiophen-2-yl]-phenoxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

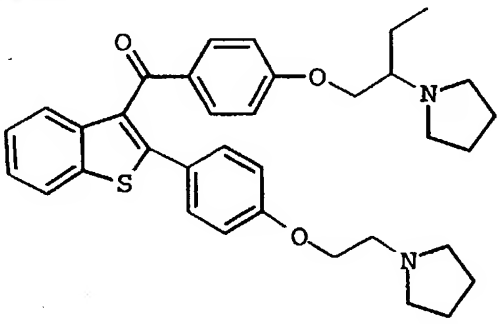
Part A. 2-(1-Pyrrolidinyl)butanol.



The title compound was prepared in 64% yield for 2 steps from pyrrolidine and ethyl 2-bromobutyrate by essentially following the procedure detailed in Example 121, Part A.

FDMS 144 (M+1); Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.23; H, 11.36; N, 9.58.

Part B. 4-[2-(1-Pyrrolidinyl)butoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



2 $C_2H_2O_4$

The title compound was prepared in 59% yield from the product of Part A and 4-fluorophenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thien-3-yl ketone by essentially following the procedure detailed in Example 121, Part B. A sample was converted to the dioxalate salt according to the method described in Example 1, Part C.

FDMS 569 (M+1); Anal. Calcd for $C_{35}H_{40}N_2O_3S \cdot 2\ C_2H_2O_4$: C, 62.55; H, 5.92; N, 3.74. Found: C, 62.39; H, 5.80; N, 3.59.

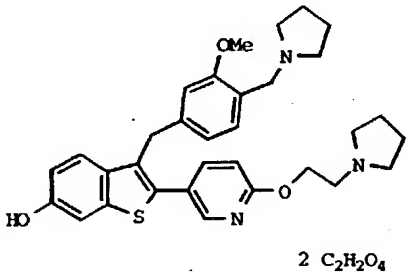
Part C. 1-[2-[4-[3-[[4-[2-(1-pyrrolidinyl)butoxy]]-phenyl]methyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]-pyrrolidine Dioxalate.

The title compound was prepared from the free base of the ketone from Part C in 76% yield by essentially following the procedure described in Example 121, Part C.

FDMS 555 (M+1); Anal. calcd for $C_{35}H_{42}N_2O_2S \cdot 2C_2H_2O_4$: C, 63.74; H, 6.31; N, 3.81. Found: C, 63.64; H, 6.07; N, 3.70.

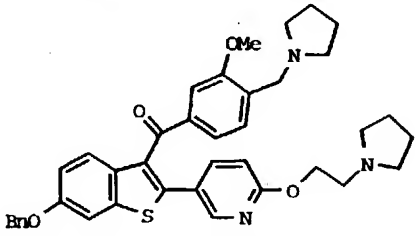
Example 123

Preparation of 1-[2-[[5-[6-Hydroxy-3-[[3-methoxy-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]pyrid-2-yl]oxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

Part A. 6-Benzyloxy-2-[6-[2-(1-pyrrolidinyl)ethoxy]-pyrid-3-yl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.

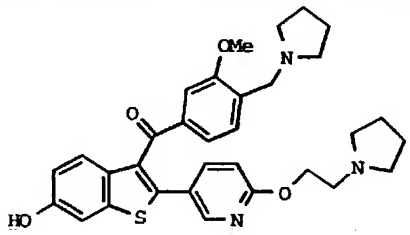


A -78 °C solution of 5-bromopyrid-2-yl 2-(1-pyrrolidinyl)ethyl ether (3.25 g, 12.0 mmol) in 40 mL of

anhydrous THF was treated with *n*-BuLi (8.1 mL, 13.0 mmol, 1.6 M in hexanes). After 1 h, a slurry of $MgBr_2$ [freshly prepared from Mg (365 mg, 15.0 mmol) and 1.3 mL of 1,2-dibromoethane] in 20 mL of anhydrous THF was added. The reaction mixture was stirred at -78 °C for an additional 10 min, and then the cold bath was removed. After 45 min, the Grignard reagent was added dropwise via a cannula to a solution of 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-methoxy-4-[(1-pyrrolidinyl)methyl]phenyl ketone (5 g, 10.0 mmol) in 50 mL of THF at 0 °C. The resulting mixture was stirred for 2 h at 0 °C and then was allowed to warm to ambient temperature. After 5 h, the reaction mixture was poured into 200 mL of saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by PrepLC (SiO_2; gradient of 85:10:5 hexanes-THF-TEA to 75:20:5 hexanes-THF-TEA) afforded 2.9 g (4.48 mmol; 45%) of the title product as a viscous orange oil.

FAB HRMS: m/e, calcd for $C_{39}H_{42}N_3O_4S$: 648.2896; Found: 648.2889 (M+1).

Part B. 6-Hydroxy-2-[6-[2-(1-pyrrolidinyl)ethoxy]-pyrid-3-yl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

The ketone (2.9 g; 4.48 mmol) from Part A in 40 mL of THF at ambient temperature was treated with 20 mL of ammonium formate (25% aqueous) and 10% Pd/C (2.9 g). Three additional 20 mL aliquots of 25% ammonium formate were added over 12 h.

The reaction mixture was filtered through a pad of diatomaceous earth, rinsing well with $CHCl_3$. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 2.08 g of the crude product as a yellow foam. Purification by radial chromatography (SiO_2; gradient of 75:20:5 hexanes-THF-TEA to 60:35:5 hexanes-THF-TEA) yielded 1.23 g (2.21 mmol; 48%) of a pale yellow foam. A sample of the free base was converted to the title dioxalate salt according to the procedure outlined in Example 1, part C.

FDMS 558 (M+1); Anal. calcd for $C_{32}H_{35}N_3O_4S \cdot 2C_2H_2O_4$: C, 58.61; H, 5.32; N, 5.70. Found: C, 58.76; H, 5.36; N, 5.80.

Part C. 1-[2-[[5-[6-Hydroxy-3-[[3-methoxy-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]pyrid-2-yl]oxy]ethyl]pyrrolidine Dioxalate.

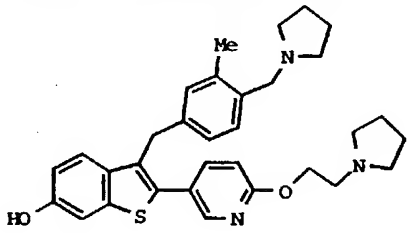
DIBAL-H (4.6 mL, 4.6 mmol, 1.0 M solution in toluene) was added dropwise via a syringe to a 0 °C solution of the ketone (Part B; 1.02 g, 1.83 mmol) in 20 mL of anhydrous THF. After 45 min, the excess DIBAL-H was quenched with excess MeOH (approximately 1 mL). A solution of 30 mL of saturated Na^+K^+ tartrate and 30 mL of EtOAc were added, and the biphasic mixture was vigorously stirred overnight at ambient temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated to an off-white foam. The crude benzyl alcohol (1.1 g) was taken up in 20 mL of 1,2-dichloroethane. Et_3SiH (2 mL, 12.8 mmol) was added, and the resulting mixture was cooled to 0 °C. After 5 min, the solution was treated with TFA (1.4 mL, 18.3 mmol). A gummy precipitate formed immediately, so the reaction mixture was allowed to warm to ambient temperature in order to re-dissolve the gum. After 3 h, the reaction mixture was poured into 100 mL of saturated aqueous $NaHCO_3$ solution. Upon addition of 50 mL of EtOAc, the product

gummed out; 15 mL MeOH and 50 ml of $CHCl_3$ were added to solubilize the product. The aqueous phase was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated *in vacuo*. Purification by radial chromatography gave 673 mg (1.24 mmol; 68%) of a white foam. The free base in 10 mL of THF was converted to the title dioxalate salt by treatment with oxalic acid (230 mg, 2.55 mmol) in 5 mL EtOAc. The white solid was filtered and dried *in vacuo* to give the title compound.

FDMS 544 (M+1); Anal. calcd for $C_{32}H_{37}N_3O_3S \cdot 2C_2H_2O_4$: C, 59.74; H, 5.71; N, 5.81. Found: C, 59.46; H, 5.70; N, 5.72.

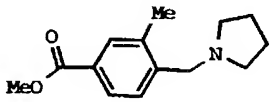
Example 124

Preparation of 1-[2-[[5-[6-Hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]pyrid-2-yloxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

Part A. Methyl 3-Methyl-4-[(1-pyrrolidinyl)methyl]-benzoate.

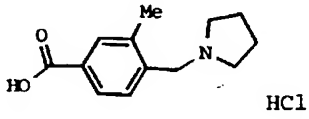


A solution of methyl 3-bromo-4-[(1-pyrrolidinyl)methyl]-benzoate (16 g, 53.7 mmol) in 110 mL of toluene was treated with $Pd(PPh_3)_4$ (3.1 g, 2.68 mmol) and tetramethyltin (22.3 mL, 161.1 mmol). The resulting mixture was heated at 135-140 °C for 36 hr in a sealed tube. After cooling to ambient temperature, the reaction mixture was filtered through diatomaceous earth and concentrated *in vacuo*. The crude brown residue was purified by PrepLC (SiO_2; 97:2:1 hexanes-

THF-TEA) to afford 11.4 g (48.9 mmol; 91%) of the title compound as a slightly yellow oil.

FDMS 233 (M^+); Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.08; H, 8.21; N, 6.00. Found: C, 72.29; H, 8.17; N, 5.91.

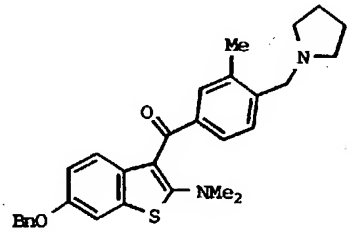
Part B. 3-Methyl-4-[(1-pyrrolidinyl)methyl]benzoic Acid Hydrochloride.



A solution of methyl 3-methyl-4-[(1-pyrrolidinyl)-methyl]benzoate (16 g, 68.6 mmol) in 250 mL of 1 N HCl was heated at reflux overnight (13 hr). After cooling to ambient temperature, the aqueous solution was extracted with EtOAc (150 mL). The aqueous layer was concentrated by rotary evaporation to give 16.8 g (65.7 mmol; 96%) of the title acid as a white solid.

FDMS 219 (M^+); Anal. calcd for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.06; H, 6.70; N, 5.48. Found: C, 61.22; H, 6.93; N, 5.37.

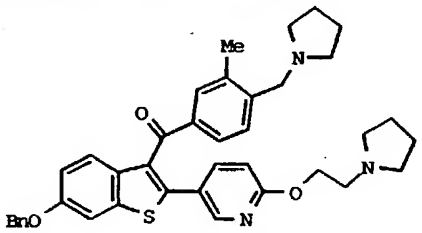
Part C. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-Methyl-4-(1-pyrrolidinylmethyl)phenyl Ketone.



The title compound was prepared from 3-methyl-4-[(1-pyrrolidinyl)methyl]benzoic acid HCl (Part B) in 80% yield as a brilliant orange solid by essentially following the procedure described in Example 39, Part B.

FDMS 484 (M^+); Anal. calcd for $C_{30}H_{32}N_2O_2S \cdot HCl$: C, 69.15; H, 6.38; N, 5.38. Found: C, 69.36; H, 6.39; N, 5.42.

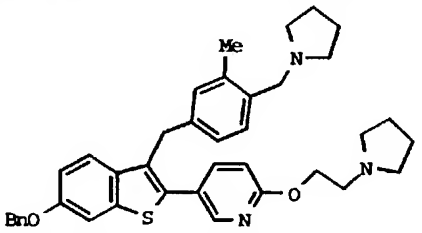
Part D. 6-Benzyloxy-2-[6-[2-(1-pyrrolidinyl)ethoxy]-pyrid-3-yl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



The title compound was prepared from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl ketone (Part C) in 32% yield by essentially following the procedure detailed in Example 123, Part A.

^1H NMR ($CDCl_3$) δ 8.19 (d, J = 2.4 Hz, 1H), 7.34-7.64 (m, 9H), 7.25 (s, 1H), 7.07 (dd, J = 8.9, 2.2 Hz, 1H), 6.99 (s, 1H), 6.62 (d, J = 8.6 Hz, 1H), 5.15 (s, 2H), 4.37 (t, J = 5.9 Hz, 2H), 3.55 (s, 2H), 2.83 (t, J = 5.9 Hz, 2H), 2.54-2.59 (br m, 4H), 2.46-2.52 (br m, 4H), 2.28 (s, 3H), 1.76-1.82 (br m, 8H); FAB HRMS: m/e, calcd for $C_{39}H_{42}N_3O_3S$: 632.2947; Found: 632.2955 (M+1).

Part E. 1-[2-[[5-[6-Benzyloxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]pyrid-2-yl]oxy]ethyl]pyrrolidine.



The title compound was prepared from the above ketone (Part D) in 47% yield by essentially following the procedure detailed in Example 123, Part C.

FDMS 618 (M+1); Anal. calcd for $C_{39}H_{43}N_3O_2S$: C, 75.82; H, 7.02; N, 6.80. Found: C, 75.64; H, 6.79; N, 6.77.

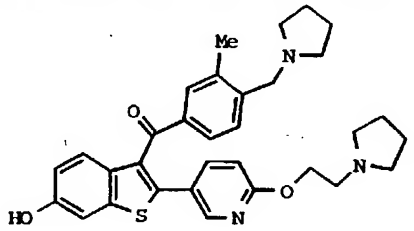
Part F. 1-[2-[[5-[6-Hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]-pyrid-2-yl]oxy]ethyl]pyrrolidine Dioxalate.

The title compound was prepared from the above benzyloxy compound (Part B) in 54% yield by essentially following the procedure described in Example 123, Part B.

FDMS 528 (M+1); Anal. calcd for $C_{32}H_{37}N_3O_2S \cdot 2C_2H_2O_4$: C, 61.09; H, 5.84; N, 5.94. Found: C, 61.04; H, 5.98; N, 5.85.

Example 125

Preparation of 6-Hydroxy-2-[6-[2-(1-pyrrolidinyl)-ethoxy]pyrid-3-yl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

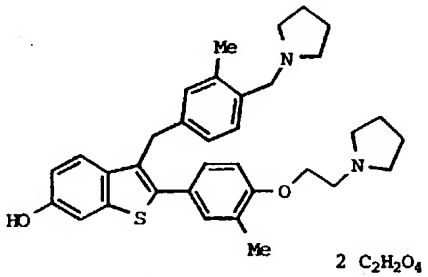
A solution of 6-benzyloxy-2-[6-[2-(1-pyrrolidinyl)-ethoxy]pyrid-3-yl]benzo[*b*]thiophen-3-yl 3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl ketone (265 mg; 0.419 mmol) from Example 124, Part D in 4 mL of 1:1 THF/EtOH was treated with 10% Pd/C (265 mg) for 11 h at ambient temperature under an atmosphere of H_2. The catalyst was filtered off and replaced with a fresh portion of 10% Pd/C (265 mg). The reaction mixture was allowed to stir for an additional 12 h under H_2 and then it was filtered through a diatomaceous earth pad. The filtrate was concentrated *in vacuo* to give 170 mg of the crude product as a yellow foam. Purification by radial chromatography (SiO_2; gradient of 2.5% to 7.5% MeOH/$CHCl_3$,

saturated with NH_4OH) afforded 75.6 mg (0.140 mmol; 33%) of a pale yellow foam which was converted to the title dioxalate salt according to the procedure outlined in Example 1, Part C.

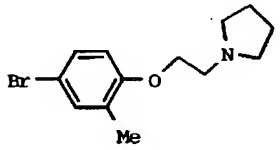
FDMS 542 (M+1); Anal. calcd for $C_{32}H_{35}N_3O_3S \cdot 2C_2H_2O_4$: C, 59.91; H, 5.45; N, 5.82. Found: C, 60.16; H, 5.53; N, 5.73.

Example 126

Preparation of 1-[2-[2-Methyl-4-[6-hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]-benzo[*b*]thiophen-2-yl]phenoxy]ethyl]pyrrolidine Dioxalate.



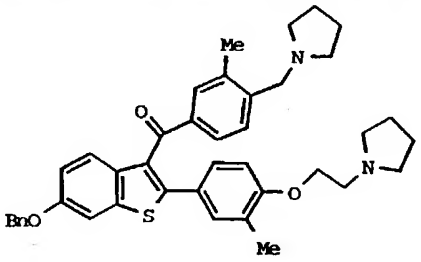
Part A. 4-Bromo-2-methylphenyl 2-(1-Pyrrolidinyl)-ethyl Ether.



4-Bromo-2-methylphenol (10 g, 53.5 mmol) and 1-(2-chloroethyl)pyrrolidine HCl (11 g, 64.7 mmol) were heated at 80 °C in 500 mL of DMF in the presence of K_2CO_3 (22 g, 159.2 mmol) for 16 h. After cooling, the crude product was filtered and concentrated *in vacuo*. The brown oily residue was purified by PrepLC (SiO_2; gradient of 90:8:2 to 85:10:5 hexanes-THF-TEA) to afford 11.25 g (39.6 mmol; 74%) of the title compound as a clear, colorless oil.

FDMS 283 (M-1), 285 (M+1); Anal. calcd for $C_{13}H_{18}BrNO$: C, 54.94; H, 6.38; N, 4.93. Found: C, 55.11; H, 6.16; N, 5.03.

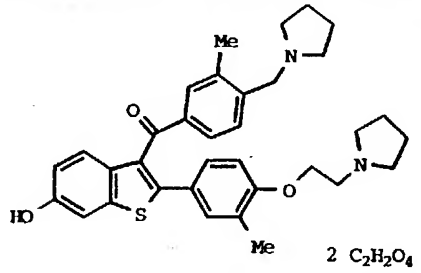
Part B. 6-Benzyloxy-2-[3-methyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



The title compound was prepared from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl ketone (Example 124, Part C) and 4-bromo-2-methylphenyl 2-(1-pyrrolidinyl)ethyl ether (Part A) in 59% yield after PrepLC (SiO_2; gradient of 85:10:5 to 75:20:5 hexanes-THF-TEA) by essentially following the procedure detailed in Example 123, Part A.

FDMS:644 (M^+); Anal. cald for $C_{41}H_{44}N_2O_3S$: C, 76.36; H, 6.88; N, 4.34. Found: C, 76.48; H, 7.13; N, 4.16.

Part C. 6-Hydroxy-2-[3-methyl-4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



The title compound was prepared from the ketone (Part B) in 66% yield after radial chromatography (SiO_2; gradient of 1% to 2% MeOH in $CHCl_3$, saturated with NH_4OH) by essentially following the procedure detailed in Example 123, Part B.

FDMS 555 (M+1); Anal. calcd for $C_{34}H_{38}N_2O_3S \cdot 2C_2H_2O_4$: C, 62.11; H, 5.76; N, 3.81. Found: C, 61.91; H, 5.92; N, 3.62.

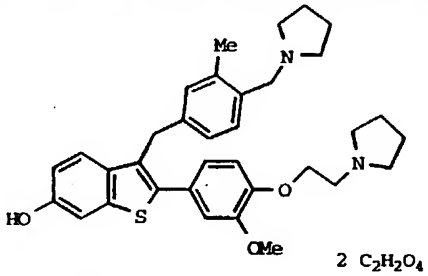
Part D. 1-[2-[2-Methyl-4-[6-hydroxy-3-[[3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]pyrrolidine Dioxalate.

The title compound was prepared from the ketone (Part C) in 62% yield after radial chromatography (SiO_2; gradient of 1% to 2% MeOH in $CHCl_3$, saturated with NH_4OH) by essentially following the procedure detailed in Example 123, Part C.

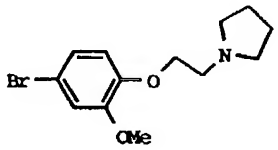
FDMS 541 (M+1); Anal. calcd for $C_{34}H_{40}N_2O_2S \cdot 2C_2H_2O_4$: C, 63.32; H, 6.15; N, 3.89. Found: C, 63.26; H, 6.39; N, 3.96.

Example 127

Preparation of 1-[[4-[6-Hydroxy-2-[3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl-2-methylphenyl]methyl]pyrrolidine Dioxalate.



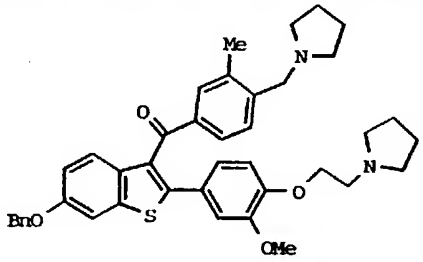
Part A. 4-Bromo-2-methoxyphenyl 2-(1-Pyrrolidinyl)-ethyl Ether.



The title compound was prepared from 4-bromoguaiacol (4-bromo-2-methoxyphenol) in 67% yield by essentially following the procedure outlined in Example 126, Part A.

FDMS 299 (M-1), 301 (M+1); Anal. calcd for $C_{13}H_{18}BrNO_2$: C, 52.01; H, 6.04; N, 4.67. Found: C, 52.24; H, 5.97; N, 4.62.

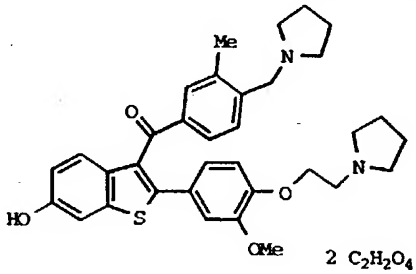
Part B. 6-Benzyloxy-2-[3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



The title compound was prepared from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-methyl-4-[(1-pyrrolidinyl)methyl]phenyl ketone (Example 124, Part C) and 4-bromo-2-methoxyphenyl 2-(1-pyrrolidinyl)ethyl ether (Part A) in 30% yield after PrepLC (SiO_2; gradient of 80:15:5 to 70:25:5 hexanes-THF-TEA) by essentially following the procedure detailed in Example 123, Part A.

^1H NMR ($CDCl_3$) δ 7.67 (d, J = 8.9 Hz, 1H), 7.63 (s, 1H), 7.39-7.58 (m, 7H), 7.27 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 9.0, 2.3, 1H), 7.00 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.20 (s, 2H), 4.12 (t, J = 6.5 Hz, 2H), 3.73 (s, 3H), 3.57 (s, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.62-2.66 (br m, 4H), 2.48-2.54 (br m, 4H), 2.29 (s, 3H), 1.80-1.84 (br m, 8H); FAB HRMS: m/e, calcd for $C_{41}H_{45}N_2O_4S$: 661.3100; Found: 661.3107 (M+1).

Part C. 6-Hydroxy-2-[3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



2 $C_2H_2O_4$

The title compound was prepared from the ketone (Part B) in 56% yield after radial chromatography (SiO_2; gradient of 1% to 2% MeOH in $CHCl_3$, saturated with NH_4OH) by essentially following the procedure outlined in Example 123, Part B.

FDMS 571 (M+1); Anal. calcd for $C_{34}H_{38}N_2O_4S \cdot 2C_2H_2O_4$: C, 60.79; H, 5.64; N, 3.73. Found: C, 60.60; H, 5.48; N, 3.63.

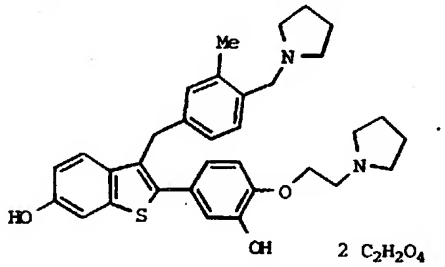
Part D. 1-[[4-[6-Hydroxy-2-[3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl-2-methylphenyl]methyl]pyrrolidine Dioxalate.

The title compound was prepared from the ketone (Part C) in 77% yield after radial chromatography (SiO_2; gradient of 1% to 2% MeOH in $CHCl_3$, saturated with NH_4OH) by essentially following the procedure described in Example 123, Part C.

FDMS 557 (M+1); Anal. calcd for $C_{34}H_{40}N_2O_3S \cdot 2C_2H_2O_4$: C, 61.94; H, 6.02; N, 3.80. Found: C, 61.65; H, 5.93; N, 3.84.

Example 128

Preparation of 1-[2-[2-Hydroxy-4-[6-hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]pyrrolidine Dioxalate.



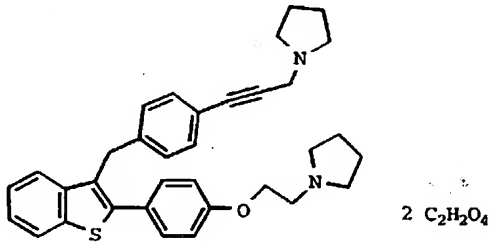
A solution of 1-[[4-[6-hydroxy-2-[3-methoxy-4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl-2-methylphenyl]methyl]pyrrolidine (Example 127, Part D; 182 mg, 0.327 mmol) in 5 mL of 1,2-dichloroethane was cooled to 0 °C and treated with EtSH (195 µL, 2.62 mmol) followed by $AlCl_3$ (262 mg, 1.96 mmol). The resulting mixture was allowed to warm to ambient temperature. After 16 h, the reaction

mixture was poured into 10 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 5% MeOH/$CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by radial chromatography (SiO_2; gradient of 1% to 4% MeOH in $CHCl_3$, saturated with NH_4OH) gave 96 mg (0.177 mmol; 54%) of a white foam. Subsequent dioxalate salt formation as described in Example 1, Part C afforded the title compound as a white solid.

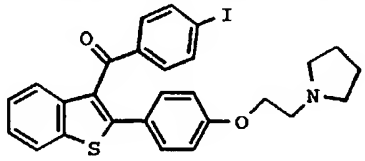
FDMS 543 (M+1); Anal. calcd for $C_{33}H_{38}N_2O_3S \cdot 2C_2H_2O_4$: C, 61.48; H, 5.86; N, 3.88. Found: C, 61.36; H, 5.77; N, 3.85.

Example 129

Preparation of 1-[2-[4-[3-[4-[3-(1-Pyrrolidinyl)-1-propynyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]-pyrrolidine Dioxalate.



Part A. 4-Iodophenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl Ketone.

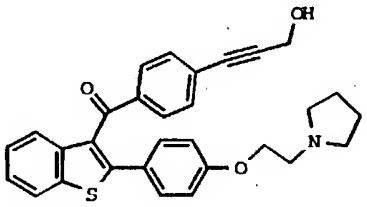


A slurry of 4-iodobenzoic acid (7.67 g, 30.9 mmol) in 300 mL of 1,2-dichloroethane and 2 drops of DMF was treated with $SOCl_2$ (11.3 mL, 154.6 mmol). The resulting mixture was heated at reflux overnight. The clear solution was evaporated *in vacuo*, then the solid residue was resuspended in 1,2-dichloroethane and reconcentrated. The crude acid chloride was dissolved in 300 mL of 1,2-dichloroethane, and 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (5.0

g, 15.5 mmol) was added. The solution was cooled to 0 °C and treated with $TiCl_4$ (8.5 mL, 77.3 mmol). After 5.5 h, the reaction mixture was carefully poured into 600 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (3 x 300 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by PrepLC (SiO_2; 1% MeOH in $CHCl_3$, saturated with NH_4OH) afforded 6.79 g (12.3 mmol; 79%) of the title product as a yellow foam.

FDMS 553 (M^+); Anal. calcd for $C_{27}H_{24}INO_2S$: C, 58.59; H, 4.37; N, 2.53. Found: C, 58.32; H, 4.28; N, 2.46.

Part B. 4-[3-Hydroxy-1-propynyl]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.

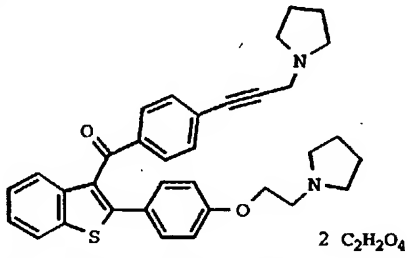


A solution of 4-iodophenyl 2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (Part A; 5.0 g, 9.0 mmol) was treated with propargyl alcohol (1.05 mL, 18.1 mmol) and $Pd(PPh_3)_2Cl_2$ (190 mg, 0.27 mmol). The reaction vessel was covered with aluminum foil to keep out light, and CuI (35 mg, 0.18 mmol) was added. After stirring overnight at ambient temperature, the reaction mixture was filtered over diatomaceous earth and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; 4% MeOH in $CHCl_3$, saturated with NH_4OH) gave 4.32 g (8.97 mmol; quantitative) of the title product as a light brown foam.

^1H NMR ($CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.38-7.42 (m, 3H), 7.16-7.22 (m, 3H), 6.66 (d, J = 8.7 Hz, 2H), 4.95 (br, 1H), 4.41 (s, 2H), 4.11 (t, J = 5.4 Hz, 2H), 2.98 (t, J = 5.4 Hz, 2H),

2.76 (br m, 4H), 1.87 (br m, 4H); FAB HRMS: m/e, calcd for $C_{30}H_{28}NO_3S$: 482.1790; Found: 482.1779 (M+1).

Part C. 4-[3-(1-Pyrrolidinyl)-1-propynyl]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



TEA (70 µL, 0.51 mmol) was added to a 0 °C suspension of the ketone (Part B; 4.9 g, 10.2 mmol) and K_2CO_3 (1.7 g, 12.2 mmol) in 70 mL of CH_2Cl_2. After 5 min, the reaction mixture was treated with methanesulfonyl chloride (945 µL, 12.2 mmol). After 1 h at 0 °C, pyrrolidine (4.24 mL; 50.9 mmol) was quickly added. After stirring 16 h at ambient temperature, the reaction mixture was poured into 100 mL of brine. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by PrepLC (SiO_2; gradient of 80:15:5 to 60:35:5 hexanes-THF-TEA) afforded 3.0 g (5.61 mmol; 51%) of a light brown foam. A sample of the free base was converted to the title dioxalate salt according to the conditions outlined in Example 1, Part C.

FDMS 534 (M^+); Anal. calcd for $C_{34}H_{34}N_2O_2S \cdot 2C_2H_2O_4$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.61; H, 5.55; N, 4.01.

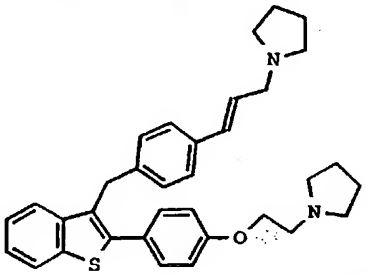
Part D. 1-[2-[4-[3-[4-[3-(1-Pyrrolidinyl)-1-propynyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]-ethyl]pyrrolidine Dioxalate.

The title compound was prepared from the ketone (Part C) in 76% yield by essentially following the procedure described in Example 133, Part C.

^1H NMR ($CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.29-7.33 (m, 4H), 7.07 (d, J = 8.1, 2H), 6.94 (d, J = 8.7 Hz, 2H), 4.24 (s, 2H), 4.14 (t, J = 6.0 Hz, 2H), 3.61 (s, 2H), 2.93 (t, J = 5.9 Hz, 2H), 2.65-2.68 (br m, 8H), 1.8-1.84 (br m, 8H); FDMS 521 (M+1); Anal. calcd for $C_{34}H_{36}N_2OS \cdot 2C_2H_2O_4 \cdot 0.2H_2O$: C, 64.79; H, 5.78; N, 3.98. Found: C, 64.42; H, 5.42; N, 3.77.

Example 130

Preparation of (*E*)-1-[2-[4-[3-[4-[3-(1-Pyrrolidinyl)-1-propenyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]-ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

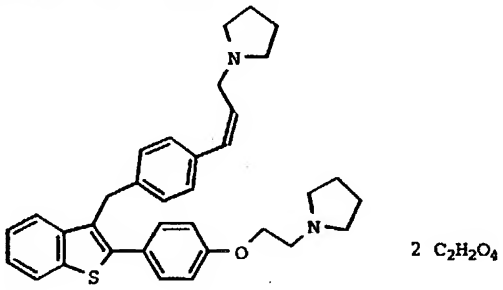
A solution of 1-[2-[4-[3-[4-[3-(1-pyrrolidinyl)-1-propynyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]-pyrrolidine (Example 129, Part D; 95 mg, 0.182 mmol) in 1.5 mL of toluene was treated with DIBAL-H (455 mL, 0.455 mmol; 1 M in toluene). The resulting mixture was heated at 40 °C for 3 h. The reaction mixture was cooled to 0 °C and quenched with excess MeOH. Saturated K^+ Na^+ tartrate solution and EtOAc (10 mL each) were added, and the biphasic mixture was vigorously stirred for 2 h. The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by radial chromatography (SiO_2; 98:1.5:0.5 $CHCl_3$-MeOH-NH_4OH) afforded 42 mg (0.80 mmol, 44%)

of a pale yellow oil which was converted to the dioxalate salt according to the methods detailed in Example 1, Part C.

^1H NMR ($CDCl_3$) δ 7.83 (d, J = 7.0 Hz, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 7.0 Hz, 2H), 7.26-7.32 (m, 4H), 7.09 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 15.9 Hz, 1H), 6.29 (dt, J = 15.9, 6.5 Hz, 1H), 4.25 (s, 2H), 4.13 (t, J = 5.9 Hz, 2H), 3.24 (d, J = 6.5 Hz, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.61 (br m, 4H), 2.54 (br m, 4H), 1.82 (br m, 8H); Anal. calcd for $C_{34}H_{38}N_2OS \cdot 2C_2H_2O_4 \cdot 0.5H_2O$: C, 64.11; H, 6.09; N, 3.94. Found: C, 64.11; H, 6.00; N, 4.08; FAB HRMS: m/e, calcd for $C_{34}H_{39}N_2OS$: 523.2783; Found: 523.2774 (M+1).

Example 131

Preparation of (*Z*)-1-[2-[4-[3-[4-[3-(1-Pyrrolidinyl)-1-propenyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]-ethyl]pyrrolidine Dioxalate.



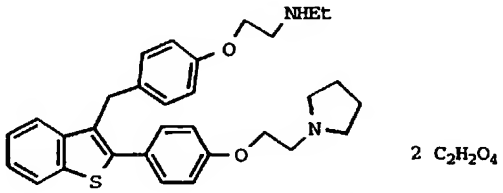
A solution of 1-[2-[4-[3-[4-[3-(1-pyrrolidinyl)-1-propynyl]benzyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]-pyrrolidine (Example 129, Part D; 300 mg, 0.576 mmol) in 40 mL of pyridine was treated with a slurry of Lindlar catalyst ($Pd/CaCO_3$, Pb poisoned; 100 mg) in 10 mL of pyridine. The resulting mixture was stirred under an atmospheric pressure of H_2 at room temperature for 3 h. The reaction mixture was filtered through a pad of diatomaceous earth and concentrated *in vacuo*. Purification by radial chromatography (SiO_2; 5% MeOH in $CHCl_3$, saturated with NH_4OH) gave 185 mg (0.354 mmol, 61%) of a yellow oil which was converted to the dioxalate

salt according to the procedure described in Example 1, Part C.

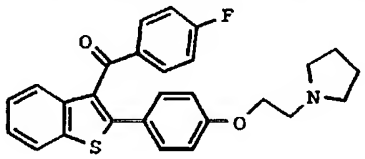
^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 6.6 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.27-7.30 (m, 2H), 7.11-7.18 (m, 4H), 6.95 (d, J = 8.7 Hz, 2H), 6.46 (d, J = 11.8 Hz, 1H), 5.81 (dt, J = 11.8, 5.9 Hz, 1H), 4.27 (s, 2H), 4.13 (t, J = 6.0 Hz, 2H), 3.40 (d, J = 6.1 Hz, 2H), 2.92 (t, J = 5.9 Hz, 2H), 2.64 (br m, 4H), 2.57 (br m, 4H), 1.76-1.84 (br m, 8H); Anal. calcd for $C_{34}H_{38}N_2OS \cdot 1.6C_2H_2O_4$: C, 67.01; H, 6.23; N, 4.20. Found: C, 66.95; H, 6.07; N, 3.88; FAB HRMS: m/e, calcd for $C_{34}H_{39}N_2OS$: 523.2783; Found: 523.2779 (M+1).

Example 132

Preparation of 1-[2-[4-[3-[4-[2-(Ethylamino)ethoxy]-benzyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]pyrrolidine Dioxalate.



Part A. 4-Fluorophenyl 2-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



The title compound was prepared in 65% yield from 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene and 4-fluorobenzoyl chloride by essentially following the procedure detailed in Example 129, Part A.

FAB HRMS: m/e, calcd for $C_{27}H_{25}FNO_2S$: 446.1590; Found: 446.1597 (M+1).